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DYSPHAGIA WITH DISORDERS OF THE HEART AND GREAT VESSELS.

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An instance of difficulty in swallowing associated with great enlargement of the left auricle (to be described below) drew our attention to the whole question of dysphagia in disorders of the heart and aorta. Since most of the easily accessible statements are inadequate, a brief review of the subject seems in order. It may be said in advance that dysphagia has been described in the following cardiovascular conditions: 1, Dilation of the left auricle (usually with mitral stenosis); 2, pericarditis; 3, saccular aneurysm; 4, dissecting aneurysm; and 5, anomalies of the aortic arch or of the great vessels springing from it. The difficulty in swallowing is usually related to direct pressure on the esophagus (see below) but marked compression frequently exists without any interference with deglutition; in fact dysphagia in cardiovascular disease is a rare event.

The term "dysphagia" has been applied in the literature not only to actual *difficulty* in swallowing but also to *pain on swallowing* without any feeling of obstruction. Dysphagia may be due to compression or to spasm. In the latter event, the contraction is mediated reflexly through the vagus. In either case, as will be seen below, symptoms may be persistent or transient. In order to understand the various clinical conditions which will be described it is important to have in mind the relations of the various cardiac chambers, the aorta and the pulmonary artery and veins to the vagus, recurrent laryngeal nerve, trachea and esophagus. These are pictured in

the following dissections (Figs. 1 and 2). In Figure 1 the close relation of the arch of the aorta and of the whole thoracic aorta to the esophagus is well demonstrated, and in Figure 2 one sees how the left auricle lies in contact with the gullet.

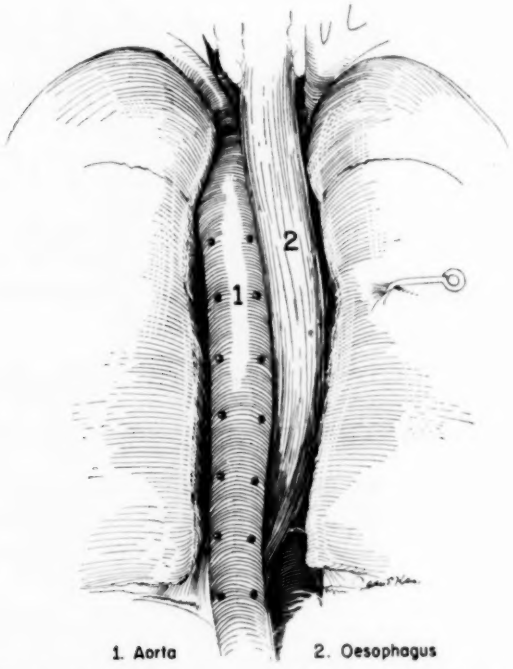

FIG. 1.—Relation of aorta to esophagus. (After Sibson.)

Dysphagia From Pressure of Dilated Left Auricle. Great dilation of the left auricle with mitral stenosis is the subject of quite a voluminous literature, and the question of big auricles in relation to recurrent laryngeal nerve palsy and to hoarseness has been especially discussed. One may refer to the article of Kovacs and Stoerk[13] who describe the relations of the esophagus to cardiac enlargement and point out that compression practically never gives rise to dysphagia because of the elasticity and motility of the tube. Excellent papers on the anatomy of big left auricles are also those of Stoerk,[34] whose illustrations have been frequently copied in the literature, and of Steele and Paterson.[33] The cuts here modified from those of Stoerk (Figs. 3, 4 and 5) show very well that the left auricle really has a posterior position and that it impinges, when enlarged, directly on the esophagus as well as upward against the bronchi which may be gouged apart just below the bifurcation. The radiologic literature also is rich in studies of these relations which are particularly well

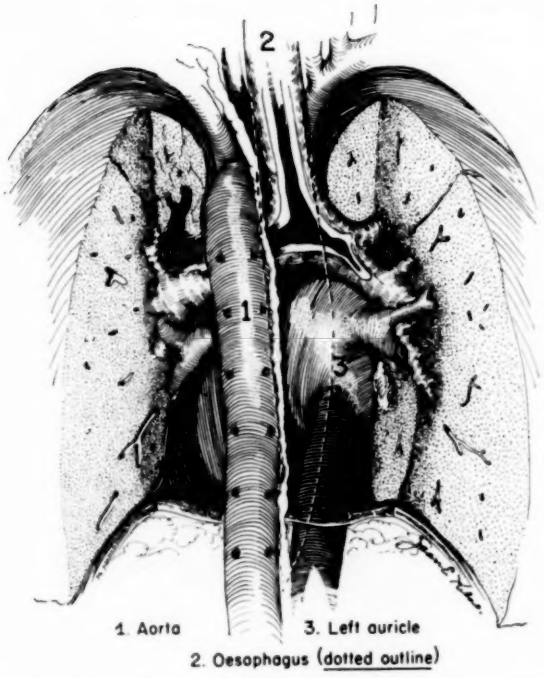

FIG. 2.—Relation of left auricle to esophagus. (After Sibson.)

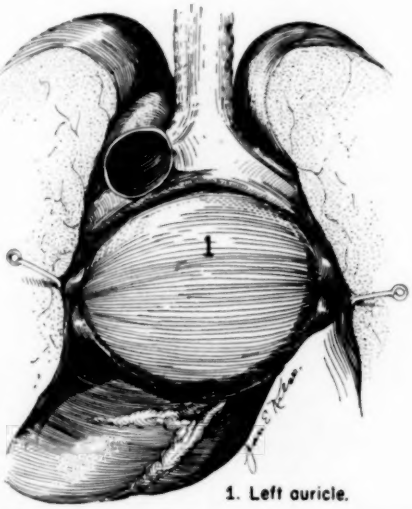

FIG. 3.—Diagram showing large left auricle pressing on bifurcation of the trachea. (Modified from Stoerk.)

exposed by Rösler and Weiss.[24] That compression of the esophagus by an enlarged left auricle is common enough is shown by radiograms to be found in every Roentgen ray laboratory and reproduced in all

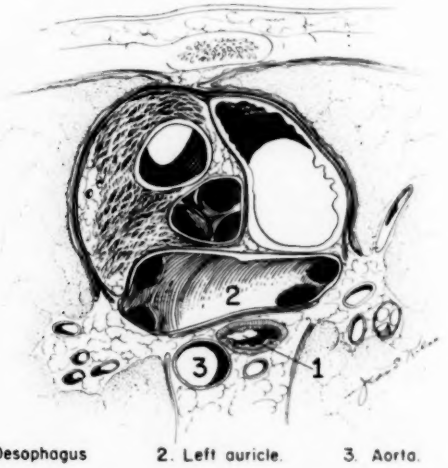

FIG. 4.—Diagram of section through heart, showing posterior portion of left auricle in relation to aorta and esophagus. (Modified from Stoerk.)

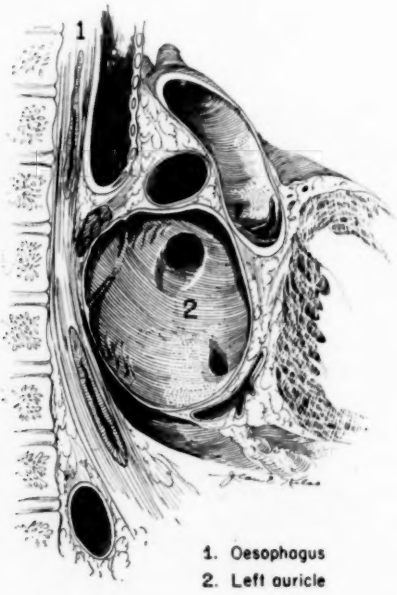

FIG. 5.—Diagram showing large left auricle from a case of mitral stenosis pressing on esophagus. (After Stoerk.)

FIG. 6.—Patient G. A. showing compression of the esophagus by the left auricle and stasis of barium.

the textbooks of cardiology. The radiogram from our patient is typical. Finally one may refer to such articles as those of Bland, Balboni and White[5] who describe the extraordinary capacity attained by dilated auricles. They point out that figures of over a liter have been reported in several cases.

But while compression of the esophagus by the auricle often occurs, clinical dysphagia from this cause is excessively rare. Dysphagia is mentioned, to be sure, in textbooks but only as part of a catalogue of symptoms handed on from one writer to another without any basis of actual experience. As a matter of fact, aside from our case, we have found only two instances in the literature: Cases 1 and 4 of Rösler. The first of these for a year had difficulty in swallowing even water; Roentgen ray demonstrated definite arrest of the barium in a dilated esophagus above the point of pressure. In the other case, there was difficulty only on excitement or exercise, but the Roentgen ray showed delay in passage of barium. Steele and Paterson[33] remark that dysphagia from auricular pressure is "common in the experience of many" but they report no cases of their own nor can we find mention of dysphagia in the papers to which they allude. Notkin[17] in a clinical abstract of 70 cases of big auricle with hoarseness found no mention of dysphagia and in the Index Medicus from 1927 to 1939 there is only one suggestive title,[36] unfortunately not accessible, in a Czech journal.

Case Report. G. A. (A92950), a 37-year-old Chinese waiter, entered the Stanford Clinic on November 1, 1939, with the complaints of shortness of breath and pain and difficulty in swallowing. About 13 months ago he began to be conscious of palpitation which was present all the time but was worse on exertion. He was, however, able to go on with his work as a waiter. There was no cough or edema, and his general health was unimpaired. In July, 1939, about 4 months ago, he began to have a sense of discomfort in the lower substernal region on swallowing. It seemed as though the food passed down more slowly than usual and while passing it caused pain or soreness. Frequently 8 or 10 minutes after swallowing he would regurgitate a portion of the food which did not taste sour. He thinks liquid food caused less soreness than a full diet. After 2 months the symptoms subsided, but about 2 weeks ago the pain on swallowing returned and has been present ever since. He has also become more short of breath although he still has no cough, edema or abdominal pain.

On examination he was neither short of breath nor cyanotic as he lay in bed. There were classical signs of mitral stenosis with great enlargement of the heart. There were no signs of pulmonary edema or of congestive cardiac failure.

Roentgen ray study by Dr. Leef on November 3d showed that when the patient swallowed barium the column was pushed back by the enlarged heart and the passage of barium through the esophagus was slow because of this pressure. A film (Fig. 6) showed an immense heart with especial enlargement of the left auricle.

On rest and venesection he improved rapidly and within a few days the dysphagia was less marked and at times disappeared. On November 10th further Roentgen ray studies by Dr. Newell were reported as follows:

"Dr. Bloomfield, Dr. Chamberlain, Dr. Olsen and Dr. Norwood looked over my shoulder while I studied the patient again fluoroscopically. Along

the left border one could make out 4 arches, counting from below upward, the left ventricle, the left auricle, the pulmonary artery and the aorta. Pulsation of the pulmonary artery is not so very marked, even as seen more prominently when the patient turns slightly into anterior oblique. The left auricle as seen in anterior projection occupies two or three times the space ordinarily occupied by the left auricular appendix, and pulsates visibly.

"Still looking with the patient straight front, we see on the lower right border a see-saw motion, the lower portion being evidently right auricle, the upper portion left auricle which is blown out with every systole by regurgitation through the mitral valve. The pulmonary vessels pulsate much more than normal, especially at the right hilum.

"On turning the patient in the left anterior oblique, and true oblique, the thickness of the heart is seen to be very great, so that it cannot be separated from the spine.

"On this occasion the patient swallows thick and thin barium mixture with the greatest of ease. The appearance of the esophagus is perfectly normal. It is indented at the aortic arch and behind the left auricle, of course. The width of the esophagus when the patient drinks barium rapidly, lying supine, is about two and one-half centimeters. As seen in lateral view with the patient lying on his side, drinking thin barium rapidly, the esophagus is seen to be only a few millimeters through from front to back behind the left auricle, although it reaches a diameter of a couple of centimeters above this. In left anterior oblique the course of the esophagus passing the left auricle shows very nicely how much it bulges to the left and backward above the left ventricle."

The patient was discharged on November 14th still complaining of a slight feeling of difficulty on swallowing.

It was the impression of those who studied the case that the dysphagia was due to spasm of the esophagus secondary to pressure by the enlarged auricle, rather than to actual obstruction.

Dysphagia With Pericarditis. Most textbooks include dysphagia among the possible symptoms of pericarditis but give no detailed data. It seemed of interest therefore to turn to the periodical literature. Smith and Willius[31] in a clinical analysis of 113 cases of pericarditis make no mention of dysphagia, nor do Camp and White[6] in a study of 106 cases. Harvey and Whilehill[11] in a recent article on tuberculosis of the pericardium also have nothing to say on trouble with swallowing. In the Quarterly Cumulative Index from 1927 to 1939 we found only one allusion to the subject, a brief case report by Rutherford[25] of an old woman with dry pericarditis who had severe pain on swallowing which disappeared as she got well. Capps makes no allusion to dysphagia in his monograph on pericardial pain.[7]

The paucity of information in the modern literature is in contrast to the detailed accounts of dysphagia with pericarditis to be found in the older treatises. Testa (Delle Malattie del Cuore, Bologna, 1811) is given credit by Walshe[37] for first describing this difficulty but Stokes[35a] criticizes the case reports and believes the dysphagia was due to cervical abscesses. Stokes further informs us that a thorough search of the works of Senac, Corvisart, Bertin, Laennec, Bouillaud, Hope and Andral yields no allusion to dysphagia. Stokes

himself, on the other hand, refers to a woman of 60 with pericarditis and "as the mouthful of food or drink passed . . . . it excited a feeling of tearing or burning . . . . which immediately subsided on the ingesta reaching the stomach" (p. 55). Walshe states that he has seen some five or six very striking examples. Sibson[30] distinguishes clearly between discomfort on swallowing presumably due to irritation of the inflamed pericardium by the bolus of food as it passes down the esophagus and actual obstruction of the tube by a distended sac. "There was difficulty or pain in swallowing in 13 of my cases of rheumatic pericarditis. . . . I have already spoken of cases in which the act of deglutition caused pain over the back of the inflamed pericardium, generally complained of, however, in the chest, by the pressure of the morsel of food upon the inflamed structures. . . . . The difficulty in swallowing, of which I now speak, occurs when the pericardial sac is distended to the full with fluid, and is caused by the compression of the esophagus between the swollen sac and the spinal column. . . . . when the patient lies flat the weight of the fluid in the pericardium falls backward with full pressure upon the esophagus and deglutition becomes more difficult; when, however, he is raised into the sitting posture, and especially if he leans forward the volume of the liquid tends forward and downward and swallowing is more easy." One patient "when the amount of effusion into the pericardium was great, swallowed more easily when the shoulders were raised than when she was lying flat." The subject is further developed along these lines by Roberts.[22]

In summary, then, dysphagia with pericarditis seems to be a rare event. Actual difficulty in swallowing probably occurs only when the esophagus is compressed by a large effusion; hence in the presence of pericarditis dysphagia may be of practical diagnostic importance as to the amount of fluid.

Dysphagia With Saccular Aneurysm. In contrast to what has been said in connection with pericarditis and big auricle, dysphagia is recognized by all to be a frequent symptom with saccular aneurysm. But here again it has been noted that even with marked compression of the esophagus there is often no complaint of trouble on swallowing. Stokes[35b] nearly a hundred years ago gives a thorough discussion of the subject. He noted that dysphagia though not uncommon is less frequently observed than compression of the air passages. He never observed it with aneurysm of the ascending arch but did with sacs of both transverse and descending aorta. Occasionally, dysphagia was the patient's sole complaint. Of special interest are Stokes' remarks on the location of discomfort on swallowing. "It is commonly referred to the middle third of the sternum, but may be felt lower down. And in the same case, as has been shown by Dr. Law, it may be referred, successively, to different portions of the tube—now at the top of the sternum, and again to the epigas-

trium." This observation we have verified in connection with pain produced by experimental distention of the esophagus.[20] "The difficulty of deglutition varies from complete dysphagia, which is rare, to the slightest feeling of obstruction; generally fluids are most easily swallowed. The sensation may be merely one of pain. . . . . The attempt to swallow often produces a paroxysm, compounded of retching, convulsive hiccough, laryngeal cough, and dysphagia." Nothing worthy of note has been added by subsequent writers. Powell[21] observed cases of aneurysm in which an actual perforation of the esophagus occurred without preceding dysphagia. Balfour[2] suggested that slight difficulty in swallowing arose from some interference with esophageal innervation rather than from actual compression. He also notes that aneurysmal dysphagia varies from time to time, that it is increased by any "excitement of the circulation," and that it may be relieved by leaning forward. Osler[19] felt that actual compression was unusual and that dysphagia was due to spasm via the vagus. Modern texts have much less to say; White,[39a] for example, makes bare mention of dysphagia along with a list of other symptoms. Turning to recent clinical reports, Sanford[27] in a series of 71 cases noted dysphagia in 14; in 2 cases it was the main symptom. Kampmeier[12] among 633 instances of saccular aneurysm found dysphagia in 11%, whereas Mills and Horton[16] in a somewhat comparable study of 339 cases noted this symptom in only 1.2%. Unfortunately no individual case reports are given.

Among our own material are 2 cases of aneurysm in which dysphagia was a notable symptom. In one the patient was unable to swallow solid food and liquids went down only with difficulty; at autopsy, there was an aneurysm of the ascending arch, compression of the trachea, and a false aneurysm with infiltration of blood about the esophagus. In the second case, the man complained of both discomfort and difficulty on swallowing; *post mortem*, there was aneurysmal dilation of the ascending, transverse and descending thoracic aorta with erosion of the aneurysm into the mediastinum and esophagus. In Stokes' most striking case, also, a man with severe prolonged aneurysmal dysphagia, there was found at autopsy a large false aneurysm with the esophagus "strongly compressed by this tumour."

In summary, then, several points of interest emerge: it appears that mild dysphagia, usually due to reflex esophageal spasm, is common with aneurysm and of no serious import; severe persistent dysphagia seems to indicate false aneurysm, or threatened rupture into esophagus, in brief, a condition of the greatest gravity. Such dysphagia in the presence of aneurysm has, therefore, considerable diagnostic and prognostic importance.

Dysphagia With Anomalies of the Great Vessels. Dysphagia with right-sided aortic arch, double aortic arch, and aberrant right subclavian artery has been so well described and the mechanism is so

simple that we shall make only brief reference to it here. The papers of Arkin[1] and of Metzger and Ostrum[15] may be consulted for excellent radiograms and diagrams of the anomalies. Suffice it to say that the aberrant vessel causes the symptoms by compression or displacement of the esophagus from behind. Diagnosis can often be made by Roentgen ray and the paper by Arkin is especially thorough from this standpoint.

A philologic digression may be allowed in connection with the term *dysphagia lusoria* which is so frequently applied to the troubles of deglutition encountered with these anomalies. Sprague, Ernlund and Albright[32] attribute the term to Bayford (1789) and point out that *lusoria* is derived from Latin *lusor*, a deceiver; White[39b] refers in this connection to "*dysphagia* (called *lusoria*, from the Latin, meaning deceitful)." Now deceitful dysphagia is meaningless, if not actually nonsense, and some other explanation of the term is required. The expression is obviously a variety of *ellipsis*, common in Latin and Greek, and in medical terms derived from those languages; one thinks quite readily of such expressions as tabes mesenterica, keratitis neuroparalytica, and exophthalmic goiter. The last refers, of course, not to a goiter containing eyes which protrude from it but to a goiter in a pop-eyed person. In other words, the adjective indicates some quality in the person who has the "struma" or "keratitis" of "dysphagia." Now *lusor* or *lusus* is used not only for deceit or playfulness but also for a sport or freak—*lusus naturæ*= a freak of nature—and it seems clear that *dysphagia lusoria* means not deceitful dysphagia but dysphagia in a person who has a freak condition, namely an anomaly of the great vessels. That the older writers with a classical education took this meaning for granted is witnessed by Hilton Fagge[8] who says, "So-called dysphagia lusoria demands a word of notice. The term was first applied by Dr. Bayford of Lewes to a case in which the right subclavian artery arose from the third part of the aorta, and passed to its distribution between the esophagus and trachea. This *lusus naturæ* was probably a mere coincidence since many people with these anomalies have no difficulty in swallowing."

The original report of Bayford[3] is of great interest. Jane Fordham was observed from infancy to have difficulty in swallowing. "For the last twenty years of her life this poor creature could scarcely, from day to day, muster up resolution to force down food to prevent her starving, so much was the difficulty of swallowing now increased. This difficulty she described as arising from an obstruction in that part of the esophagus which is opposite the first bone of the sternum. The food did not return when it came to that place; but seemed to make a momentary stop; and in the instant she felt an inexpressible something approaching to strangulation or suffocation which she could only compare to the conceived agonies of death. Upon these occasions she always experienced violent palpitations of the heart.

I was by accident upon the spot at the time of her death; and having heard the above history of her case, I felt myself interested in making a further enquiry into the cause of the obstruction by an examination of the dead body. . . . . If the reasoning which I have used upon this occasion be at all conclusive, and the unusual situation of the right subclavian artery be considered as the sole cause of the obstruction in deglutition; a new species of dysphagia is hereby established, which may be called *lusoria* from the *Lusus naturæ* that gives rise to it."

Dissecting Aneurysm. Pressure on the esophagus by the false sac must be a common event in cases of dissecting aneurysm, but clinical dysphagia rarely occurs. As with some of the disorders we have already discussed, general statements about trouble with swallowing are to be found but specific case reports are rare. Shennan,[29a] for example, in his excellent monograph on dissecting aneurysms notes that "In addition to the cases complaining of choking sensations or as if some foreign body had stuck in the throat, there are other cases which complain of difficulty of swallowing, this resulting from direct pressure of the sac upon the esophagus or from involvement of the inferior laryngeal." But no mention of dysphagia is found in the case reports of Shennan's 17 patients. Gager[9] and McGeachy and Paullin[14a] in their analysis of several hundred cases quote no specific instances. We have also looked up the reports of 60 cases[4,10,14b,18,23,26,28,29b,38] in recent papers without finding definite mention of difficulty on swallowing. It may be that dysphagia is overshadowed by other more desperate symptoms such as pain and collapse, or perhaps inquiry is not usually made. At any rate, dysphagia plays no important part in the symptomatology of dissecting aneurysm, although careful questioning as to its presence would be of interest in suspected cases and might help in differentiating from coronary occlusion.

Summary. 1. Dysphagia may occur in connection with the following disorders of the heart and aorta: Dilated left auricle, pericarditis, saccular aneurysm, dissecting aneurysm and anomalous aortic arch.

2. While pressure on the esophagus is common with all these conditions, clinical dysphagia occurs very rarely except with saccular aneurysm and anomalous aortic arch.

3. Difficulty in swallowing with pericarditis suggests a large effusion.

4. Marked dysphagia with aneurysm suggests a false sac or huge lesion with threatened rupture.

5. Dysphagia in a supposed case of coronary occlusion should arouse suspicion of dissecting aneurysm.

6. The literature dealing with the above conditions is reviewed and a case of dysphagia associated with compression of the esophagus by an enlarged left auricle is reported.

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FURTHER EXPERIENCE WITH GLOBIN INSULIN.

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Recently published results[1] indicate that in some moderately severe and severe cases of diabetes, globin insulin has advantages over protamine insulin. The following data on 4 severe cases afford further confirmation.

Case Abstracts. Case 1 (No. 593117).—A man, aged 57, entered the hospital for amputation of the foot due to diabetic gangrene. Although an exceptionally severe diabetic, he had consistently neglected diet and insulin

for 13 years, and overindulged in alcohol. He had marked diabetic retinitis and arteriosclerosis. During the 10 days preceding operation his diet was 150 carbohydrate, 80 protein, and 100 fat, and he received protamine insulin beginning with 40 units and increasing to 100 units each morning, together with varying amounts of regular insulin. Yet he passed sugar continuously with blood values ranging between 210 and 344 mg. per 100 cc. After the operation protamine insulin was increased to 120 units a day and as much as 90 units of regular insulin was given in addition without any effect; that is, all specimens contained maximum amounts of sugar. On November 28 120 units of globin insulin and 55 units of regular insulin were administered and at 4:30 P.M. he was sugar-free for the first time and his blood sugar was 135 mg. per 100 cc. On the following day he was sugar-free but on November 30 he began to run a temperature, and from then until December 11 he was uncontrolled, though he received as much as 200 units of globin insulin and 60 units of regular. However, since December 11 his control has gradually returned on 200 units of globin insulin and 60 of regular insulin, so that on the day of discharge, December 27, his blood sugars at 11:30 and 4:30 were 116 and 114 mg. per 100 cc., respectively, and he was sugar-free. At the present time (February 8, 1940) he is taking 20 units of regular insulin and 200 units of globin insulin each morning with absence of sugar in all specimens.

TABLE 1.—DATA OF CASE 1.

Date, 1939.	Insulin.	Units.	Urine sugars.	Blood sugars.
11/27	Protamine	120	6 A.M.—++++	Fasting—224
	Regular	90	11 A.M.—++++	
			1 P.M.—++++	
			7 P.M.— +++	
			9 P.M.— +++	
11/29	Globin	120	6 A.M.— 0	11:30 A.M.—158
			11 A.M.— 0	4:30 P.M.—166
1940.			9 P.M.— 0	
2/8	Globin	200	6 A.M.— 0	
	Regular	20	11 A.M.— 0	
			9 P.M.— 0	

TABLE 2.—DATA OF CASE 2.

Date, 1939.	Insulin.	Units.	Urine sugars.
10/26	Protamine	98	6–11 A.M.—++++
			11–5 P.M.—++++
			5–9 P.M.—++++
			9–6 A.M.—++++
10/27	Protamine	98	6–11 A.M.—++++
			11–5 P.M.—++++
			5–9 P.M.—++++
			9–6 A.M.—++++
10/28	Globin	80	6–11 A.M.— 0
			11–5 P.M.— 0
			5–9 P.M.— 0
			9–6 A.M.— 0
10/29	Globin	75	6–11 A.M.— 0
			11–5 P.M.— 0
			5–9 P.M.— +
			9–6 A.M.— 0
10/30	Globin	75	6–11 A.M.— 0
			11–5 P.M.— 0
			5–9 P.M.— 0
Diet, 300–100–180.			9–6 A.M.— 0

CASE 2 (No. 588526).—A man, aged 20, was admitted in acidosis on September 10 with a CO_2 of 12, and discharged on November 1, 1939. During this time he received 200 carbohydrate, 70 protein, and 100 fat daily. Later this was increased to 300 carbohydrate, and from October 4 until his discharge he received 300 carbohydrate, 100 protein and 180 fat. He was unregulated on 98 units of protamine insulin until October 28. On the 28th he received 80 units of globin insulin, and this was gradually decreased during the next 3 days to 73 units with almost complete clearing up of his glycosuria.

CASE 3 (No. 595600).—An unmarried man, colored, aged 35, has had diabetes since 1934. He came in for acidosis which responded to the usual method of treatment and then was placed on a diet of 250 carbohydrate,

TABLE 3.—DATA OF CASE 3.

Date, 1939.	Insulin.	Units.	Urine sugars.	Diet. C.	P.	F.
12/18 . . .	Protamine	82	6–11 A.M.— +	250	70	100
			11–5 P.M.— + + + +			
			5–9 P.M.— + + + +			
			9–6 A.M.— + + + +			
12/19 . . .	Protamine	82	6–11 A.M.— + + + +			
	Standard	15	11–5 P.M.— + + + +			
			5–9 P.M.— + + + +			
			9–6 A.M.— + + + +			
12/28 . . .	Globin	70	6–11 A.M.— + +	300	70	100
			11–5 P.M.— 0			
			5–9 P.M.— +			
			9–6 A.M.— 0			
12/29 . . .	Globin	72	6–11 A.M.— 0			
			11–5 P.M.— 0			
			5–9 P.M.— 0			
			9–6 A.M.— 0			

TABLE 4.—DATA OF CASE 4.

Date, 1940.	Insulin.	Units.	Urine sugar.	Blood sugar.	Diet. C.	P.	F.
1/17	Protamine	60	6–11 A.M.— +		200	70	100
			11–5 P.M.— +				
			5–9 P.M.— + +				
			9–6 A.M.— 0				
1/18	Protamine	60	6–11 A.M.— +				
			11–5 P.M.— + +				
			5–9 P.M.— + +				
			9–6 A.M.— + + +				
1/19	Protamine	60	6–11 A.M.— +				
			11–5 P.M.— 0				
			5–9 P.M.— +				
			9–6 A.M.— +				
1/30	Globin	35	6–11 A.M.— +		250	70	100
			11–5 P.M.— 0				
			5–9 P.M.— +				
			9–6 P.M.— +				
1/31	Globin	30	6–11 A.M.— +				
			11–5 P.M.— 0				
			5–9 P.M.— +				
			9–6 A.M.— +				
2/1	Globin	30	6–11 A.M.— 0				
			11–5 P.M.— 0	11:30—85			
			5–9 P.M.— 0	4:30—60			
			9–6 A.M.— 0				

70 protein and 100 fat daily, and was given protamine insulin with standard insulin, in amounts up to 82 units of protamine and 60 units of standard insulin without any effect on the glycosuria. This period lasted 10 days. He then was given a single dose of 80 units of globin insulin. This was followed by an immediate clearing up of his sugar and the occurrence of insulin shocks. The insulin was finally reduced to 72 units a day, and all specimens became sugar-free.

CASE 4 (No. 581009).—A colored laundress of 58 with marked hypertension. Diabetic symptoms came rather suddenly about 7 months ago. She was tried on protamine insulin up to 60 units a day for about a week with fair regulation, then shifted to 60 units of globin insulin, with marked improvement. Having abnormally low blood sugars and symptoms of insulin shock, it was apparent that she required considerably less globin insulin. The dose was reduced by half, and the diet increased from 200–70–100 to 250–90–100. Now she requires 30 units of globin insulin to make her sugar-free most of the time.

The following is a table of the sugar excretion for about 1 month of a diabetic boy of 16 (No. 583702) who has been on globin insulin since May, 1938. At present he receives a single dose of 94 units each morning.

TABLE 5.—DATA ON CASE NO. 583702. URINE SUGAR DETERMINATIONS.

Date, 1940.	12 M. to 8 A.M.	8 A.M. to 12 N.	12 N. to 4 P.M.	4 P.M. to 8 P.M.	8 P.M. to 12 M.	Remarks.
2/1	0	0	0	0	0	
2/2	0	0	0	0	0	
2/3	0	+	++	0	0	
2/4	+	+	0	0	0	
2/5	0	0	0	0	0	Very weak—2 lumps sugar
2/6	0	0	0	0	+	
2/7	+	+	0	0	0	
2/8	+	+	0	0	0	
2/9	0	0	0	0	0	
2/10	0	0	0	+	+	
2/11	0	0	0	0	0	Felt weak
2/12	0	++	+	+	+	
2/13	0	0	0	0	0	
2/14	0	0	++	+++	+++	Shocked
2/15	0	0	0	0	0	
2/16	0	+	0	0	0	
2/17	0	0	+	0	0	
2/18	0	+	0	+	0	
2/19	0	0	0	0	0	
2/20	0	0	+	+	0	
2/21	+	+	0	0	0	
2/22	0	0	0	0	0	
2/23	0	+	0	0	0	
2/24	0	0	+	0	+	
2/25	0	0	0	0	0	
2/26	0	+	0	0	0	
2/27	0	0	+	0	0	
2/28	0	0	0	0	0	
2/29	0	0	0	0	0	
3/1	0	+	0	+	0	
3/2	0	0	0	0	0	
3/3	0	0	0	0	0	
3/4	+	0	0	0	+	

The following table summarizes our experience with globin insulin:

TABLE 6.—PATIENTS RECEIVING GLOBIN INSULIN TO MARCH, 1940.

History No.	No. of units. Initial.	No. of units. Present.	No. of months on globin insulin.	Diet. C.	Diet. P.	Diet. F.	Urine sugar last visit. Fasting.	Urine sugar last visit. 11:30.	Urine sugar last visit. 4:30.	Urine sugar last visit. 10:00.	Blood sugar last visit, 11:30 A.M.
457353	50	46	20	200	70	100	++++				147*
581009	60	30	2	250	90	100	0	0	0	0	75
457988	80	74	4	150	60	90	++++	+++	+	++	144
245926	88	72	28	140	80	80	0	+	0	0	183
71851	80	75	21	310	70	100	+	0			83
354588	70	64	27	175	70	75	0	0	0	0	90
241966	100	48	15	200	80	90	0	0	0	0	
51008	45‡ 10§	55‡ 15§	16	175	90	120	+	0			301*
567272	50	36	14	200	80	100	0	0	0	0	85
309995	85	75	11	250	80	80	+				74
356561	35	40	24	200	90	150					
545439	70	40	18	170	80	120	0	0	0*	0	
463000	55	65	4	230	80	100	+++	++++	+++	++++†	150
68476	54	50	21	225	70	100	0	+	0		
245481	80	65	24	150	80	75	0	0	0	0	153
583702	48	90	21	250	120	150	+	+	0	0	64*
327875	110	126	15	300	110	130	0	0	0	0	172
389730	60	40	16	290	90	90	0	0	0	0	244

* Blood sugar taken at 4:30 P.M.
† Has severe cold.
‡ Globin insulin.
§ Standard insulin.

Discussion. The cases presented above show striking improvement in some instances when they are transferred from protamine zinc insulin to globin insulin. Although such improvement may be seen in the course of any insulin therapy, the marked change noted on shifting to globin insulin seems to be more than merely coincidental.

It is also to be noted that the insulin requirement of patients using globin insulin over a long period decreases in the majority of cases.

It is of interest to note that although some of these cases have received globin insulin daily for over 2 years, no case of allergy has developed. Moreover, several patients who had severe skin reactions after injections of protamine zinc insulin, such as redness, urticaria and infiltration, were promptly relieved of this condition when changed to globin insulin.

Thanks are due to the Burroughs Wellcome & Co. Experimental Research Laboratories, who kindly furnished the globin insulin, and to Drs. Edgar Stillman and Bertram Sanger for their coöperation, and to Miss Ruth Husing for the laboratory work.

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LEVULOSURIA.

A Study of Two Cases in Brothers.

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Biologic anomalies include certain metabolic functional disorders which are detected by chemical examination of body fluids. The many types of sugars taken in the human food offer possibilities for the occurrence of instances of partial or absolute inability of the organism to metabolize any one of them. Aberrations of dextrose metabolism occurring in the young may be accompanied by changes in the number or cell structure of the islets of Langerhans of the pancreas. Pentose and levulose (fructose) have been recognized in the urine of persons who have no definite signs of disease, but who display a remarkable defect in their lack of ability to convert either of these sugars into glycogen.

Levulose, a levorotatory monosaccharide, is present in considerable amount in fruits and honey, and is formed in the break-up of cane sugar. It reduces Benedict's and Fehling's solutions, behaving like dextrose in this respect except that reduction proceeds in the cold as well as with heat. It forms a brown precipitate with hydrochloric acid and resorcinol (Seliwanoff's test). Its osazone crystals are characteristic and have a constant melting point. With these means of identification, levulosuria is being detected more frequently, although only 31 cases have appeared in the literature.

Two cases of levulosuria in brothers have recently come under my observation.

Case 1.—A Jewish boy of 14, at birth weighed 5 pounds and was a full term child. Sugar was said to have been found in his urine at $2\frac{1}{2}$ years when his tonsils and adenoids were removed. His diet had been restricted more or less since, and there were episodes every 2 to 3 months of vomiting and occasionally "air hunger." He had been under the care of 12 doctors at different times with a diagnosis of diabetes mellitus. He had had insulin on two occasions for short periods. Nothing is known about the blood sugar levels except 8 years ago when he was in the Albany Hospital for observation. Normal figures were observed at the same time that melliturla was present. For the past 10 years under restricted diet his weight has been subnormal. In June, 1938, his weight was 92 pounds, on July 30, 1938, $86\frac{1}{2}$ pounds. He tired easily and spent most of his time sitting and reading. However, he was an excellent student and led his class in school.

Two days previous to my first seeing him (July 30, 1938), he had a severe vomiting spell and in a 6-day period had lost 6 pounds. His mother assumed that his diabetes was out of control, although carbohydrates had been much restricted for several years. There had never been any excessive hunger, thirst, or polyuria.

Physical Examination. An underweight boy, $61\frac{1}{4}$ inches tall, weight $83\frac{1}{2}$ pounds. The heart showed a loud systolic murmur at mitral and aortic areas, transmitted slightly into the neck, but with no thrill. Second aortic

and pulmonic sounds somewhat snapping in character. The examination otherwise disclosed nothing abnormal.

Laboratory Examination. Hemoglobin, 86%; blood pressure, 134-90; pulse, 84, regular. Urine: pale; specific gravity, 1.005; sugar, ++; albumin, slight trace. Sediment, negative. Blood sugar at 3 P.M., 154 mg.

Blood Wassermann reaction was negative.

He was admitted to the Samaritan Hospital, July 31, 1938, for investigation of his mellituria. While in the hospital he was given an 1800 cal. diet: C-130; P-75; F-98, and insulin u10–u10–u10. Later this was changed to u20 of protamine zinc insulin. The mellituria continued, and gradually the insulin was increased to u45 and the diet changed to C-142; P-75; F-85, with little effect on the urine sugar. The blood sugar at the hospital the morning after admission was 95 mg. per 100 cc. and 4 days later it was 85 mg. per 100 cc. with the urines at these times being positive for sugar. No acetone or diacetic acid was ever found. It was suspected that the case was not diabetes, but mellituria of another nature. Several different urine specimens were examined by the Seliwanoff test for fructose, and found positive. The phenylhydrazine test showed crystals of glucose or fructose present, but none of other sugars. The sugar was fermented by yeast. A specimen of urine submitted to Prof. Arthur Bray of Rensselaer Polytechnic Institute and others examined by Prof. Arthur Knudson of Albany Medical College were found to rotate polarized light to the left.

Further studies were made from time to time, the mellituria persisting.

September 22, 1938, 24-hour specimen of urine: acid reaction; on a diet devoid of fruits or cane sugar, contained no sugar.

October 7, 1938, basal metabolic rate + 13%. Weight 94½ pounds.

November 2, 1938, he felt very well. Urine sugar+++. Mitral murmur had disappeared. P_2 accentuated only slightly.

December 3, 1938, weight 101½ pounds. Blood pressure 112/58; pulse 90. Systolic murmur at mitral area, not transmitted.

October 15, 1938, dextrose tolerance test showed a normal curve.

October 20, 1938, fructose tolerance test using 56 gm.

Blood Sugar	Mg. per 100 cc.
Fasting	84
30 min. after 56 gm. of fructose	109
2 hrs. after 56 gm. of fructose	125
3 hrs. after 56 gm. of fructose	117

Urine Sugar (at the above periods):	Output (cc.)	Fructose (gm.)
Fasting		0.0
30 min. after 56 gm. of fructose	44	0.5
1 hr. after 56 gm. of fructose	24	0.8
2 hrs. after 56 gm. of fructose	48	0.8
3 hrs. after 56 gm. of fructose	40	1.9
	156	4.0

During 1939 his weight increased to 112 pounds. He now feels normal in every way. The mitral murmur has disappeared. The mellituria has persisted. The urine before breakfast is negative to Benedict's test, or contains only a trace of sugar. The sugar reduces Benedict's solution in the cold as well as with heat. During the day it is constantly present. A small amount of fruit is consumed, but so far there have been no apparent unfavorable symptoms.

His weight on February 21, 1940, was 119¼ pounds, a total gain of 33 pounds since July 30, 1938. Height had increased 1½ inches. Blood pres-

sure 112 to 120 systolic, 60 to 65 diastolic. Pulse 66 to 90. A systolic murmur was heard occasionally at apex and base. Occasionally the urine contained a faint trace of albumin, but no renal elements in the sediment. Urea clearance test normal.

On February 20, 1940, using Roe's method for blood levulose the following determinations were made 2 hours after lunch:

Blood Dextrose.	Blood Levulose.	Urine Dextrose.	Urine Levulose.
96.1 mg.	7.5 mg.	3+	3+

On the basis of the above findings, the patient was advised to eat generously and get his weight and strength back as much as possible. He and his parents were rather skeptical of this advice after so many doctors had told him he had diabetes and to beware of starches and sugars. Nevertheless, with only a slight restriction of fruits he followed this régime and his weight and strength returned rapidly. He graduated a year later from Intermediate School leading his class in scholarship and taking part in many physical activities he had formerly been denied.

CASE 2.—The familial history of Case 1 revealed that the mother and father were living and well, although of a very nervous type. One brother died of tuberculosis following whooping cough at the age of 30. Another brother, aged 20, had been suspected recently of having sugar in his urine and the following is his story.

He is the next oldest brother to Case 1, rather shy, highly nervous, and plays the violin in a symphony orchestra. He had been attending a boy's camp for 2 months and was losing weight steadily because his physician had told him he had "sugar diabetes," and carbohydrates were removed almost entirely from his diet. His maximum weight had been 140 pounds, 3 months previously. This had dropped to 115 pounds. For several months there had been furuncles on his arms, but these had recently healed.

At the age of 10 a school physician is said to have noted a murmur in his heart. In high school his pulse rate was frequently around 95. He finished high school in 1937. There is no history of rheumatic fever, scarlet fever, pneumonia or typhoid, or other serious illness. His habits are good. He takes no exercise in addition to his work which is largely clerical, or delivering dry goods in an automobile. His only other complaint is a rather excessive shyness and frequent palpitation of the heart. There has never been excessive thirst, hunger, pruritus, or urinary frequency.

On physical examination his height was 5 feet 10 inches; weight 115 pounds, average normal 152 pounds. The reflexes were hyperactive. His heart showed a blowing systolic murmur, loudest at the mitral and aortic areas, transmitted into the axilla, but not into the neck. No thrill could be detected. P_2 was not accentuated. The pulse rate in my office was 110 to 120, and regular. Blood pressure was 178/70. Blood Wassermann reaction was negative.

The postprandial urine gave a 3+ reaction for sugar, and 1+ for albumin. The sediment showed a moderate number of hyaline and granular casts and a few leukocytes. The sugar in the urine was fermented by yeast, and reduced Benedict's reagent in the cold as well as with heat. Seliwanoff's and Bouchardt's tests were positive and the osazone test was positive for glucose or levulose (the crystals are similar). Urine specimens rotated polarized light to the left.

A dextrose tolerance test gave the following result:

	Blood sugar.	Urine sugar.
Fasting	95	Negative
30 min. after 100 gm. glucose	135	Negative
60 min. after 100 gm. glucose	157	Negative
150 min. after 100 gm. glucose	75	Negative

On a diet of C-180; P-75; F-95; glycosuria was pronounced. Five units of protamine zinc insulin did not affect the condition, nor did 20 units daily. The urine remained constantly negative just before meals and strongly positive for sugar after meals. He omitted insulin for 2 days, ate anything he wished and then showed a normal dextrose tolerance test. On a general diet he gained 5 pounds in 12 days, during which time the blood sugar remained within normal limits, the highest figure 116 mg. per 100 cc. In 24 hours an output of 2 quarts of urine contained 5.5 gm. of sugar.

The blood pressure was always elevated, varying from 152 to 184 systolic, 50 to 70 diastolic. The pulse rate was 110 to 140. The dextrose tolerance test on October 15, 1938, was normal. A levulose tolerance test gave the following results:

Blood Sugar	Mg. per 100 cc.
Fasting	80.0
30 min. after taking 56 gm. of levulose	106.0
1 hour after taking 56 gm. of levulose	107.0
2 hours after taking 56 gm. of levulose	133.3
3 hours after taking 56 gm. of levulose	129.0

Urine Specimens (at the above periods):

Fasting: Acetone and diacetic acid, 0; Sugar, 0.

	Specific gravity.	Output cc.	Sugar gm.
30 min.	1.017	65	.34
1 hr.	1.015	63	1.05
2 hr.	1.024	90	3.15
3 hr.	1.028	110	3.30
	Total	328	7.84

The basal metabolism was +12%. He always showed tachycardia in the presence of his physician, but insisted his pulse rate and nervousness were much less when elsewhere than in a doctor's office. There was a loud systolic murmur at the apex. Numerous urine tests in addition to sugar revealed a trace of albumin and hyaline casts, a few granular casts and a few leukocytes. Urea clearance test was normal.

An electrocardiogram showed right axis deviation and sinus tachycardia.

Between September 10, 1938, and February, 1940, on a general diet, with no restrictions except for no excess of fruits and honey, his weight increased from 117½ pounds to 134½ pounds. He now feels strong, works steadily, and looks in the best of health in contrast to the thin, rather emaciated physique of 2 years ago.

On February 6, 1940, using Roe's method for blood levulose, the following determinations were made:

	Blood Dextrose mg. per 100 cc.	Blood Levulose mg. per 100 cc.	Urine Dextrose.	Urine Levulose.
Fasting	101	0.0	0	0
2 hr. after noon meal	98	5.6	3+	3+

Discussion. The data above given seem sufficient to justify the opinion that we are dealing with true levulosuria occurring in Jewish brothers and probably existing since early childhood. The error made by various physicians of regarding the mellituria as glycosuria and the disease as "diabetes mellitus" has doubtless been made many times. While only 31 cases are found in the literature, there are probably many unrecorded although recognized instances of this

interesting metabolic anomaly. In Joslin's clinic it is considered a rare condition. Root[5] writes, "We only find a very occasional case, although we test every patient with glycosuria for levulose now."

The levulosuria when undetected may be a very serious matter to the patient because of the dietary restrictions naturally adopted in the attempt at controlling the mellituria, since it is uninfluenced by insulin. My 2 cases were rapidly being reduced to a state of emaciation by carbohydrate withdrawal. A diet of generous proportions when prescribed was viewed by them and their parents with much misgiving and even alarm, after the years of diabetic discipline to which they had been subjected. Their response to adequate food was dramatic and serves to emphasize the prime importance of the blood sugar level as the basic guide in diabetic diagnosis.

These 2 cases occurring in young brothers makes it likely that there is a congenital factor involved, of relative inability to metabolize levulose, or to retain it in the blood stream long enough to be broken down and used.

The tolerance for levulose is said to be less in persons with impaired liver function, and a levulose test for liver disease is based on this idea. In the cases here reported there is nothing to suggest hepatic derangement, except this one finding of levulose in large quantities in the urine. The levulose tolerance test demonstrates adequate liver function based on the blood concentration of the sugar.

The method devised by Roe[4] for differentiating quantitatively levulose from dextrose in the blood was applied to the urine of these 2 patients. While exact weights were not determined, it was found that at the time the levulose was present in large amount in the urine (3+) an approximately equal amount of dextrose was being passed, and at a time when the total blood sugar was within normal limits. The urines were levorotatory, but this is to be expected since the levorotatory power of levulose is twice that of the dextro-power of dextrose. The latter sugar then might go unrecognized in the presence of an equal amount of levulose.

A possible explanation of the glycosuria occurring only at the same time as the levulosuria is that the kidneys permit dextrose to escape in about equal amount with the levulose, since they have the same molecular weights. In Case 2, with signs of renal irritation and arterial hypertension, the kidneys might be suspected of being more permeable to sugar than normal. Case 1, however, shows no evidence of kidney disease. Since the boys are brothers, an inherited factor is probably the basic one, although the renal element in Case 2 must be considered as possibly affecting the quantitative results, but in which direction can only be conjectured. It seems unlikely that we are dealing here with "familial-nephritic levulose diabetes."

The output of levulose in 3 hours following the ingestion of 56 gm., was 7.1% for Case 1 without renal complications, and 14% for Case 2 with hypertension and cylindruria. Fourteen per cent in

3 hours is approximately the amount noted by Silver and Reiner,[6] and Marble and Smith.[3]

The polariscope was first used in urinalysis by Biot in 1840, but von Gorup-Besanez[7] was the first to note a levorotatory sugar that behaved like fructose. Silver and Reiner[6] in 1934 found 27 cases of levulosuria reported since 1876 and added 3 of their own. They noted only 1 case of essential levulosuria in the American literature since 1912.

Following the thorough studies of Silver and Reiner, Marble and Smith in 1936 reported the one case they had found, after examining 136 consecutive specimens of urine containing sugar, a 17-year-old girl who had fructosuria with mild diabetes. All of these cases, including those of Silver and Reiner and mine, were in young people—22 years the oldest. Five cases were Jewish, and 2 of Silver and Reiner's were in Italian-born brothers.

Levulose has been found to protect slightly against the hypoglycemia of hyperinsulinism, but an analysis of the blood sugar curves in the cases reported show that in persons with levulosuria uncomplicated by diabetes mellitus the amount of levulose retained in the blood is probably so small as to be of little importance in "doubling" for dextrose.

The younger of the 2 patients may be suspected of having an old rheumatic valvular heart disease of very mild degree, not sufficient to cause any clinical cardiac disturbance, or the mitral murmur might be explained on a so-called functional basis.

The older brother, however, offers a complication which, were he the only case studied, would possibly carry much weight in explaining the urinary sugar. There is no history of rheumatic fever or scarlet fever, but he is an excellent example of paroxysmal tachycardia with hypertension. The electrocardiogram shows right axis deviation. In addition, he has albuminuria and frequently hyaline and granular casts in his urine. The blood nitrogen has always been normal, as have urea clearance tests. Nevertheless, there may be an element of increased renal permeability due to a mild degree of chronic nephritis.

The incidence of glycosuria in paroxysmal hypertension is worth discussing briefly. Labbé, Tinel, and Doumer[2] report a case of glycosuria associated with episodes of systolic pressure as high as 280 mg. Hg. Foucar[1] regards the transient glycosuria during or immediately after periods of paroxysmal hypertension as strictly renal in type, "due to the sudden increase in pressure in the 'arterial mirabile' of the kidney (glomerular tufts of the renal corpuscles, including the afferent and efferent glomerular arterioles)." He found in the literature 12 cases, in which transient glycosuria was noted only in 3, and the highest blood sugar 125 mg. per 100 cc. Most of the cases had tumors of the adrenal gland, usually pheochromatocytomas or paragangliomas. In Case 2 of the writer's, the pulse rate would reach 140 per minute and the systolic blood pressure 180 mg. Hg. Any moderate nervous strain in addition to visiting a physi-

cian's office probably produced the same reaction. It is possible that he harbors a pheochromatocytoma, but only time will throw further light on this possibility.

The great production of epinephrine by these tumors carries with it the possibility of its being liberated into the blood stream during emotional stress, or even by postural changes which might aid in expressing epinephrine from it. This sudden liberation of epinephrine produces an effect on the liver cells resulting in a rapid discharge of glycogen with resulting hyperglycemia and glycosuria. While Case 2 did not show hyperglycemia, the circumstances, including as they do paroxysmal hypertension, warrant a consideration of all facts involving sympathetic stimulation and glycogen mobilization.

Levulosuria, then, as illustrated by these 2 cases in young brothers, is probably an expression of congenital permeability of the kidneys to levulose, and based on no known anatomical lesion of the kidney, or of the liver. The occurrence of dextrose in the urine along with levulose is probably analogous to the leakage of levulose through the kidneys in reported cases of severe glycosuria in diabetes mellitus and based on purely physical factors of altered glomerular filtration.

Summary. Two cases are reported of so-called essential levulosuria in young Jewish brothers. They bring the total on record to 33. The condition appears to be a metabolic anomaly in which the organism exhibits a partial or complete inability to convert levulose into glycogen. This seems to be due not to a hepatic deficiency, but to increased permeability of the kidneys by the levulose molecule. This renal hypothesis does not postulate any inherent kidney disease, although in one case with paroxysmal hypertension there were signs of renal irritation. In both cases an approximately equal amount of glucose was excreted, but only at the same time that levulose was passing through the kidneys. Normal dextrose and levulose tolerance tests were obtained.

The clinical importance of the condition lies in its early recognition, before the patient is subjected to the rigors of a diabetic regimen which may severely handicap the growing child. The treatment is reassurance that he does not have diabetes mellitus, and a diet without special restrictions. So far as is known, the passage of levulose through the kidneys causes no harm, although continual observation of these interesting people throughout their lives may later alter this dictum in some degree.

The writer wishes to thank Dr. Stewart H. Jones for his assistance in the early study and diagnosis of these cases, and Miss Helen Lutz of the Cluett Pathological Laboratory, Samaritan Hospital, for her technical help.

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STUDIES ON THE PRESERVATION OF HUMAN BLOOD.

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In the United States human blood is commonly preserved in "banks" for transfusion by the addition of 14 cc. of a sterile 2.5% solution of chemically pure sodium citrate in physiologic saline solution to each 100 cc. of blood, giving a 0.35% concentration of sodium citrate with preservation at 4° to 6° C. in a refrigerator. Most attention has been given the matter of preservation of erythrocytes and the prevention of hemolysis but as I pointed out in 1939,[8] blood so preserved showed such rapid disintegration of neutrophils with reduction in their phagocytic activity, along with rapid disintegration of platelets and gradual loss in bactericidal activity, that preserved citrated blood was considered inadvisable for the treatment of the anemias, hemorrhagic states and infections although apparently useful in the treatment of acute hemorrhage and surgical shock.

Recently there has been an increasing appreciation of the fact that if dextrose or dextrin is added to preserved citrated blood, sodium penetration and cell swelling are decreased with inhibition of hemolysis as originally shown by Rous and Turner.[14] Thus Maizels and Whittaker[10b,c] have reported not only these effects following the addition of carbohydrates but also an increase of surface area of the erythrocytes so that they can tolerate a larger absolute inflow of fluid. Aylward and his colleagues[1] have also found that citrate-glucose preservation is not only superior to citrate alone in delaying hemolysis but that it also retards chemical changes in the cells leading to an increase of plasma inorganic phosphate with reduced plasma potassium, probably due to a lower degree of hemolysis. DeGowin, Harris and Plass[5a] have likewise found that large amounts of isotonic dextrose not only reduce hemolysis but that the erythrocytes better resist the effects of shaking and agitation. Whether or not efforts toward the prevention of hemolysis in preserved blood are a matter of practical importance, although desirable from the standpoint of therapy, cannot be stated and particularly since O'Shaughnessy and his colleagues[11] have reported that 5% solutions of hemoglobin in Ringer's solution are capable of carrying oxygen and maintaining osmotic pressure although not capable of maintaining life more than 36 hours because of rapid removal by the cells of the reticulo-endothelial system.

Belk, Henry and Rosenstein[2] have confirmed my observations on the marked and rapid disintegration of granulocytes and platelets in preserved citrated blood as well as showing increased fragility of the erythrocytes, rapid glycolysis, changes in oxygen capacity and plasma carbon dioxide. They also observed that the transfusion of hemolyzed blood produced jaundice in some cases but whether or not preservation with dextrin or dextrose with sodium citrate results in better preservation of granulocytes, platelets and the immunologic properties of plasma has not been determined.

Purpose of Investigation. Under the circumstances I have thought it advisable to determine the properties of four well-known preservatives (two without and two with carbohydrate) not only in relation to the fragility, dehemoglobinization and disintegration of erythrocytes, but likewise in relation to the preservation of leukocytes with special reference to the neutrophils and platelets as well as of prothrombin time, isoagglutinins, complement and bactericidal activity. Some attention has been given prothrombin as based upon examinations employing the method of Howell but the technique employed for the collection and preservation of blood did not permit the use of the method of Quick. Nor have I included determinations for potassium since DeGowin and his colleagues[5b] have shown that there is progressive diffusion from human erythrocytes into plasma reaching the maximum in from 15 to 20 days and because variations in sodium, chloride, citrate and dextrose in preservatives as well as different temperatures and atmospheres did not affect the rate of diffusion which cannot be explained by the release of this ion from completely hemolyzed corpuscles. Furthermore, in blood preserved for as long as 30 days it was found that the diffused potassium was not toxic nor high enough to cause significant changes in the serum potassium of the recipient.[4]

Methods. Two adult donors were selected belonging to Groups A and B and the blood of each used with the following four preservatives:

(*a*) *Sodium Citrate* (citrate):

Sodium citrate (dihydric)	2.5 gm.
Distilled water	100.0 cc.

12.6 cc. of the solution was used with 90 cc. of blood giving a final concentration of 0.35% citrate.

(*b*) *Moscow Institute of Hematology* (M.I.H.) as given by Elliott:[6]

Sodium chloride	3.5 gm.
Sodium citrate (dihydric)	2.5 "
Potassium chloride	0.1 "
Magnesium sulphate	0.002 "
Distilled water	500.0 cc.

50 cc. of the solution was used with 50 cc. of blood.

(*c*) *Modified Rous–Turner* (R–T) as described by DeGowin, Harris and Plass:[5a]

Solution A: 3.2 gm. sodium citrate (dihydric) dissolved in 100 cc. of distilled water.

Solution B: 10.8 gm. dextrose dissolved in 200 cc. of distilled water.

For use 10 cc. of Solution A and 65 cc. of Solution B were mixed with 50 cc. of blood.

(*d*) *Maizels and Whittaker* (M–W) as described by these authors:[10a]

Sodium chloride	0.43 gm.
Sodium citrate (dihydric)	1.05 "
Dextrin	8.5 "
Distilled water	100.0 cc.

For use 40 cc. of the solution was mixed with 80 cc. of blood.

Before use each preservative solution was sterilized in the Arnold sterilizer for 1 hour on each of 2 days in succession and all examined for sterility by aërobic and anaërobic cultures.

The mixtures of blood and preservative were kept in a refrigerator at 4° to 6° C. and the following 10 examinations conducted with each within 24 hours, 3, 5, 7, 10, 14 and 21 days after collection:

1. Macroscopic record of spontaneous dehemoglobinization.
2. Fragility or tonicity of erythrocytes.
3. Total erythrocyte counts.
4. Total leukocyte counts and morphologic changes in the neutrophils.
5. Differential leukocyte counts.
6. Platelet counts by the smear method.
7. Prothrombin time of the plasma (Howell method).
8. Preservation of isoagglutinins in the plasma.
9. Complement content of the plasma for sensitized sheep corpuscles.
10. Bactericidal activity of the plasma for *B. typhosus*.

Results. *Spontaneous Dehemoglobinization of Erythrocytes.* As shown in Table 1, spontaneous dehemoglobinization occurred in very much less degree over the period of 21 days in the case of the two carbohydrate-citrate preservatives than in the two without dextrose or dextrin; of the latter dextrose (modified Rous-Turner) was slightly better than dextrin (Maizels and Whittaker) in the preservation of the erythrocyte against dehemoglobinization. I use this term instead of "spontaneous hemolysis" because, as will be shortly shown in Table 4, the presence of dissolved hemoglobin in the plasma does not appear to be due entirely to hemolysis of the erythrocytes.

TABLE 1.—SPONTANEOUS DEHEMOGLOBINIZATION OF ERYTHROCYTES IN PRESERVED BLOODS KEPT AT 4° TO 6° C.

Intervals, days.	Citrate.		M.I.H.		R-T.		M-W.	
	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.
1	0*	0	0	0	0	0	0	0
3	2	2	0	0	0	0	0	0
5	3	3	2	1	0	0	0	0
7	4	3	3	2	0	0	0	0
10	4	3	3	2	0	0	1	0
14	4	4	3	3	0	0	1	1
21	4	4	3	3	0	0	1	1

* 0 = no macroscopic discoloration; 1 = very slight discoloration; 2= slight discoloration, etc.

Fragility or Tonicity of Preserved Erythrocytes. In conducting these tests a portion of each preserved blood was centrifuged and the corpuscles suspended in an equal volume of physiologic saline solution (50% suspension). One drop was added to 1.25 cc. of solutions of sodium chloride in water varying from 0.28 to 0.5% in small test tubes and the mixtures allowed to stand at room temperature for 2 hours when the readings for initial and complete hemolysis were made.

Initial hemolysis of fresh blood commonly occurs at 0.42 to 0.44% sodium chloride in the method employed and as shown in Table 2 all of the preservatives showed a slight increase of fragility at the end of 3 days' preservation (0.5% sodium chloride) which kept quite constant to 21 days.

TABLE 2.—FRAGILITY OF ERYTHROCYTES (INITIAL HEMOLYSIS) IN BLOOD KEPT AT 4° TO 6° C.

Intervals, days.	Citrate.		M.I.H.		R-T.		M-W.	
	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.
1	0.46	0.46	0.46	0.46	0.46	0.46	0.46	0.46
3	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
7	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
10	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
14	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
21	0.5	0.5	0.5	0.5	0.48	0.48	0.5	0.5

Complete hemolysis of fresh blood commonly occurs at 0.32 to 0.36% sodium chloride in the method employed and, as shown in Table 3, tonicity was fairly well preserved by all four preservatives for the period of 21 days but somewhat better by the two carrying dextrose (R–T) and dextrin (M–W) than the two without carbohydrate (citrate and M.I.H.). It would appear, therefore, that dextrose and dextrin in preservatives tend to protect the tonicity of erythrocytes.

TABLE 3.—FRAGILITY OF ERYTHROCYTES (COMPLETE HEMOLYSIS) IN BLOOD KEPT AT 4° TO 6° C.

Intervals, days.	Citrate.		M.I.H.		R-T.		M-W.	
	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B	Donor A.	Donor B.
1	0.38	0.36	0.34	0.36	0.38	0.38	0.36	0.36
3	0.38	0.38	0.38	0.38	0.38	0.38	0.38	0.38
5	0.36	0.38	0.38	0.38	0.38	0.38	0.38	0.38
7	0.36	0.40	0.38	0.38	0.36	0.36	0.38	0.38
10	0.38	0.40	0.38	0.38	0.38	0.38	0.38	0.38
14	0.40	0.40	0.40	0.40	0.38	0.38	0.38	0.38
21	0.44	0.46	0.44	0.42	0.38	0.36	0.36	0.42

Preservation of Erythrocytes. The results of total erythrocyte counts shown in Table 4 were made after gentle but thorough shaking of the mixtures. In this connection the dilution factor

TABLE 4.—PRESERVATION OF ERYTHROCYTES IN BLOOD KEPT AT 4° TO 6° C.
(Erythrocytes given in millions per c.mm.)

Intervals, days.	Citrate.		M.I.H.		R-T.		M-W.	
	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.
1	4.96*	4.92	3.27	3.15	2.85	2.15	3.75	3.64
3	4.85	4.98	2.81	2.99	2.75	2.38	3.70	3.68
5	4.68	4.85	2.80	2.85	2.29	2.09	3.63	3.50
7	4.51	4.61	2.71	2.50	2.04	2.10	3.50	3.40
10	4.29	4.33	2.60	2.40	2.32	2.19	3.37	3.46
14	4.32	4.24	2.51	2.50	2.28	2.21	3.37	3.39
21	4.16	4.07	1.83	1.75	2.26	2.15	3.43	3.46

* Per c.mm. of blood-preservative mixture.

from the volume of preservative in relation to volume of blood must be kept in mind but by reading the figures downward in the table the total erythrocyte counts may be compared at the different intervals of preservation.

Allowing for experimental error in making the counts it appears that the two carbohydrate preservatives (R–T and M–W) showed the least reduction over the period of 21 days, although closely similar results were observed with the plain citrate preservative while the M.I.H. preservative showed the poorest preservation of the four methods employed. When compared with Table 1, however, it is noted that the plain citrate preservative showed the highest degree of dehemoglobinization as judged by the discoloration of plasma, but apparently this was not entirely due to hemolysis of the erythrocytes but largely to diffusion of hemoglobin.

Preservation of Leukocytes. The results of total leukocyte counts made after gentle but thorough shaking of the mixtures are shown in Table 5. In this connection the dilution factor from the volume of preservative in relation to volume of blood must likewise be kept in mind but by reading the figures downward in the table the total counts may be compared at the different intervals of preservation.

TABLE 5.—PRESERVATION OF LEUKOCYTES IN BLOOD KEPT AT 4° TO 6° C.

Intervals, days.	Citrate.		M.I.H.		R–T.		M–W.	
	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.
1	6800*	5950	5000	3750	3300	3250	3450	2900
3	2750	2850	1400	1700	1650	2100	1850	2050
5	2750	2150	850	850	1100	1100	1600	1950
7	2550	2700	1000	550	850	1000	1400	1600
10	1700	1650	400	450	750	950	1300	1500
14	1400	1250	200	350	250	600	1400	1300
21	1000	1050	50	50	150	200	1050	800

* Per c.mm. of blood-preservative mixture.

It will be noted that in the plain citrate mixture 21 to 25% of the leukocytes had disintegrated at the end of 3 days and from 57 to 68% within 21 days. With the M.I.H. preservative about 21.2 to 36% had disintegrated in 3 days and 74 to 100% within 21 days. With the R–T preservative 15.5 to 20% had disintegrated in 3 days and 16 to 22% within 21 days. With the M–W preservative 14.1 to 18.7% had disintegrated in 3 days and 32.8 to 35% within 21 days. Of the four preservatives employed it is observed, therefore, that the leukocytes were best preserved by the R–T and M–W preservatives carrying dextrose and dextrin respectively.

As will be shortly shown, these disintegrative changes principally affected the neutrophils and is a phase of blood preservation which has received very little attention although of probable importance in relation to the transfusion treatment of acute and chronic infections if it is granted that the administration of whole leukocytes is of benefit in treatment.

The results of differential leukocyte counts giving the percentages of neutrophils in the preserved blood are shown in Table 6. It will be noted that with the plain citrate preservative from 16.1 to 23.8% had disintegrated within 3 days; 18.8 to 20.4% in the M.I.H. preservative, 14.3 to 15% in the R–T and 18.3 to 22.4% in the M–W, while in 10 to 14 days all had disintegrated in all four preservatives in confirmation of my previous observations.[8] Evidently the total leukocyte counts shown in Table 5 were mostly composed of lymphocytes and monocytes as observed in these stained smears for differential counts.

TABLE 6.—PRESERVATION OF NEUTROPHILS IN BLOOD KEPT AT 4° TO 6° C.

Intervals, days.	Citrate.		M.I.H.		R–T.		M–W.	
	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.
1	58*	57	60	53	60	66	58	55
3	36	24	32	26	40	46	26	30
5	24	24	20	26	16	12	20	24
7	8	16	12	12	12	12	12	12
10	—†	8	10	10	8	10	8	8
14	—	—	—	—	—	—	—	—
21	—	—	—	—	—	—	—	—

* Per cent. † Less than 8%.

Furthermore, as shown in Table 7, slight changes in the morphology and tinctorial properties of the neutrophils were observed in all specimens within the first 24 hours after collection of blood which became progressively more marked in 3 to 5 days and so advanced by 10 to 14 days as to render the cells scarcely recognizable.

TABLE 7.—MORPHOLOGIC CHANGES IN NEUTROPHILS IN BLOOD KEPT AT 4° TO 6° C.

Intervals, days.	Citrate.		M.I.H.		R–T.		M–W.	
	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.
1	1*	1	1	1	1	1	1	1
3	2	1	2	2	1	1	1	1
5	3	3	3	3	3	3	3	3
7	4	4	3	4	4	4	3	4
10	—	4	4	4	4	4	4	4
14	—	—	—	—	—	—	—	—
21	—	—	—	—	—	—	—	—

* 0 = morphology and staining good; 1 = slight changes; 2 = moderate changes; 3 = marked changes; 4 = severe changes; — = practically unrecognizable.

Preservation of Platelets. As stated in my former report[8] the platelets of blood preserved with plain sodium citrate showed distinct clumping immediately and 24 hours after collection with

TABLE 8.—PRESERVATION OF PLATELETS IN BLOOD KEPT AT 4° TO 6° C.

Intervals, days.	Citrate.		M.I.H.		R–T.		M–W.	
	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B
1	265,000*	280,000	277,950	281,440	248,500	237,600	217,500	253,800
3	82,450	99,600	62,660	47,840	99,000	64,740	84,400	68,760
5	56,160	53,350	58,800	37,050	50,370	45,980	45,500	40,480
7	28,260	32,270	27,100	31,570	28,560	30,560	25,410	24,800
10	28,740	27,789	28,100	31,800	20,880	19,710	26,960	22,140
14	17,680	13,020	21,280	11,280	9,140	6,630	16,850	20,340
21	—†	—	—	—	4,520	6,750	13,720	17,300

* Per c.mm. of preserved blood. † Could not be counted.

evidence of deterioration in the latter. At the end of 48 hours they became scarce and after 5 days only blue chromatin masses remained. Similar changes were observed in the present study which made their counting very difficult so that the results shown in Table 8 can be regarded as only approximately correct.

It will be noted that in the plain citrate preservative the platelets were reduced by 29 to 32% within 3 days with practically none remaining at the end of 21 days. In the M.I.H. mixtures they were reduced by 44 to 49% within 3 days and likewise practically absent at the end of 21 days. In the R–T mixtures they were reduced 25 to 36.7% within 3 days but some were countable at the end of 21 days, with similar results with the M–W preservative in that 25 to 38% had disintegrated in 3 days with some still countable at the end of 21 days. The results have indicated therefore that both carbohydrate preservatives gave somewhat better preservation of platelets.

Preservation of Prothrombin Time. As previously stated, these determinations were made by the method of Howell as the method of Quick for prothrombin could not be employed owing to technical conditions. Rhoads and Panzer[13] have stated that blood preserved for a week or more is practically useless in the treatment of the acute prothrombin deficiency encountered in jaundiced patients not adequately treated with vitamin K and bile salts. In their opinion, blood in bank for 3 days would probably be of some slight value but would be so inferior to fresh blood that they recommend that only the latter be used when transfusion is intended to combat the hemorrhagic tendency in jaundice. Ziegler[15] also found that prothrombin decreased over a period of time in preserved citrated blood kept at 34° F. to a level of 40% of original content and states that in cases in which it is desired to raise the prothrombin content of the blood by transfusion, old banked blood is not a suitable agent. Quick[12] also found that the prothrombin diminishes in decalcified blood and that it is inferior to fresh blood for controlling hemorrhage in jaundice. However, the matter may be of more academic value than practical interest, since it is thought that transfusion even with fresh blood probably raises the prothrombin content of the blood of the recipient by only 6 to 8%.

As determined by the Howell method, the normal prothrombin time is about 10 minutes and, as shown in Table 9, I found the time slightly reduced with the plasmas of all preserved bloods within 24 hours after collection of blood, presumably due to an increase of thromboplastin from disintegrated platelets. This initial decrease was followed, however, by an increase of prothrombin time with the plasmas of all preserved bloods up to 7 days and apparently due to a loss of prothrombin, but curiously this was followed by a decrease of prothrombin time during the following 10 to 21 days with the plasma from the plain citrate and M.I.H. preserved bloods, while the plasmas of the carbohydrate preserved specimens (R–T

and M–W) continued to show an increased time indicative of loss of prothrombin. In this connection it is important to state that all of our determinations were of prothrombin time (Howell) and that determinations of prothrombin by the Quick method have shown deterioration in citrate preserved blood as previously stated.

TABLE 9.—PROTHROMBIN TIME OF BLOOD AT 4° TO 6° C.

Intervals, days.	Citrate.		M.I.H.		R–T.		M–W.	
	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.
1	9*	9	9	8	8	9	9	7
3	12	10	9	11	12	8	12	9
5	12	12	12	12	12	12	14	12
7	11	11	11	11	12	11	15	11
10	10	7	9	8	13	11	12	11
14	7	7	8	8	14	12	13	12
21	7	7	8	7	14	11	9	10

* Minutes required for coagulation; method of Howell.

Preservation of Isoagglutinins. Not without interest is the question of the persistence of isoagglutinins for erythrocytes in preserved blood in relation to transfusion although Strumia, Wagner and Monaghan[15] have stated that the intravenous injection of stored plasma from citrated blood (100 cc. of 2% citrate to 500 cc. of blood) at the rate of 5.6 cc. per minute produces no reactions even though capable of agglutinating the erythrocytes of the recipient in dilutions as high as 1 to 80. Knott and Koerner,[7] however, state that citrated plasma may retain agglutinins for several weeks when kept at a low temperature and think it is advisable to test the erythrocytes of the recipient with a 1 to 50 dilution of stored 0 plasma before administration because 0 plasma sometimes contains agglutinins a and b in high concentration capable of quickly agglutinating the corpuscles of Groups A, B and AB.

In our study the plasmas of blood group Donor A were tested with the corpuscles of blood group Donor B and the plasmas of B with the corpuscles of A by the same microscopic method commonly employed in direct matching tests. As shown in Table 10 the plasma agglutination showed no evidences of diminution during the first 10 days with all four preservatives, while at the end of 14 and and 21 days' preservation some diminution occurred which was somewhat less marked in the case of the two carbohydrate preservatives (R–T and M–W). Whether this decrease of agglutination

TABLE 10.—PRESERVATION OF ISOAGGLUTININS IN BLOOD KEPT AT 4° TO 6° C.

Intervals, days.	Citrate.		M.I.H.		R–T.		M–W.	
	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.
1	4*	4	4	4	4	4	4	4
3	4	4	4	4	4	4	4	4
5	4	4	4	4	4	4	4	4
7	4	4	4	4	4	4	4	4
10	4	4	4	4	4	4	4	4
14	3	4	3	4	4	4	4	4
21	2	3	2	3	3	4	3	4

* 4 = strong agglutination; 3 = moderate agglutination; 2 = weak agglutination.

was due to diminution of agglutinins in the plasmas or to insusceptibility of preserved erythrocytes to agglutination I am unable to state.

Preservation of Complement. As previously reported,[8] the complement of citrated (0.35%) human blood, kept at 4° to 6° C., was well preserved up to 14 to 21 days. Similar results have been observed in this investigation with all four preservatives as shown in Table 11, although some loss of hemolytic complement usually occurred after 7 days of preservation.

TABLE 11.—PRESERVATION OF COMPLEMENT IN BLOOD KEPT AT 4° TO 6° C.

Intervals, days.	Citrate.		M.I.H.		R-T.		M-W.	
	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.
1	0.2*	0.2	0.3	0.3	0.3	0.3	0.3	0.3
3	0.2	0.2	0.3	0.3	0.3	0.3	0.3	0.3
5	0.2	0.2	0.3	0.3	0.3	0.5	0.3	0.3
7	0.2	0.2	0.3	0.4	0.4	0.5	0.3	0.3
10	0.2	0.2	0.4	0.4	0.5	—†	0.3	0.3
14	0.3	0.3	0.5	0.5	0.5	—	0.3	0.4
21	0.5	0.4	0.5	0.5	0.5	—	0.4	0.4

* Amounts of plasma giving complete hemolysis.

† Incomplete hemolysis with 0.5 cc. of plasma.

These tests were conducted with the following amounts of each plasma: 0.05, 0.1, 0.2, 0.3, 0.4 and 0.5 cc., placed in small test tubes with 0.5 cc. of 2% suspensions of washed sheep corpuscles and 1 cc. of 1 to 2000 antisheep hemolysin (2 units), followed by water-bath incubation at 37° C. for 1 hour when the readings were made. The smallest amounts of plasma giving complete hemolysis are shown in the table and, of course, these have varied according to the dilutions of blood with the various preservatives, but by reading the table downward it will be observed that remarkably good preservation of hemolytic complement was observed with all preservatives during at least the first 7 to 10 days.

Preservation of Bactericidal Activity. As previously reported,[8] the bactericidal activity of normal citrated (0.35%) human blood kept at 4° to 6° C. for *Staph. aureus*, beta-hemolytic streptococcus and *B. coli* decreased after 7 to 21 days' preservation. Similar results were observed in the present investigation employing *B. typhosus* as shown in Table 12.

All eight of the preserved bloods were cultured 24 hours, 3, 5, 7, 10 and 21 days after collection and found sterile. In conducting the tests at these intervals 3 cc. amounts of each plasma, secured

TABLE 12.—PRESERVATION OF BACTERICIDAL ACTIVITY OF BLOOD KEPT AT 4° TO 6° C.

Intervals, days.	Citrate.		M.I.H.		R-T.		M-W.	
	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.	Donor A.	Donor B.
1	0*	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0
7	2	0	0	0	2	3	4	4
10	3	3	3	3	3	4	4	4
21	4	4	4	4	4	4	4	4

* 0 = no growth; 2 = slight growth; 3 = moderate growth; 4 = heavy growth.

by centrifuging, were seeded with 0.1 cc. of a 1 to 10 dilution of 18-hour broth culture of *B. typhosus* and incubated along with control cultures in broth at 37° C. for 72 hours. The controls showed good growths in 24 hours, while the results observed with the various plasmas are summarized in Table 12. It will be observed that they were completely bactericidal up to about the seventh day of preservation following which rapid deterioration in bactericidal activity occurred.

Discussion. It is apparent, therefore, that none of the four preservatives employed in this investigation afford adequate protection of the neutrophilic leukocytes and platelets. This phase of blood preservation has not received the attention it deserves in relation to the transfusion treatment of the acute and chronic infections as well as, possibly, in relation to the hemorrhagic states due to prothrombin deficiency. For these reasons the author has advised against the use of blood preserved for more than 3 days[8] for these therapeutic purposes as fresh blood appears advisable.

Possibly the same applies to the transfusion treatment of the anemias, although preserved blood appears adequate for the treatment of acute hemorrhage and surgical shock. For these purposes I believe that the addition of dextrose (modified Rous-Turner) or dextrin (Maizels and Whittaker) to the preservative is advisable, as both appear to better preserve erythrocytes than plain citrate or the preservative advocated by the Moscow Institute of Hematology as likewise found by MacDonald and Stephen,[9] although Boland, Craig and Jacobs[3] believe that the M.I.H. preservative is advisable for long preservation and plain citrate for short preservation. With these conclusions I cannot agree.

Summary. 1. The preservation of the blood of 2 adult donors belonging to Groups A and B by four different preservatives up to 21 days at 4° to 6° C. has been investigated. Of the four preservatives employed two were without carbohydrate (plain citrate and Moscow Institute of Hematology), one with dextrose (modified Rous-Turner) and one with dextrin (Maizels and Whittaker).

2. Examinations were made within 24 hours and at the end of 3, 5, 7, 10, 14 and 21 days' preservation for dehemoglobinization, fragility and preservation of erythrocytes, preservation of leukocytes with special reference to the neutrophils, preservation of platelets and prothrombin and the preservation of isoagglutinins, complement and bactericidal activity.

3. The two carbohydrate preservatives gave better protection of erythrocytes against dehemoglobinization, fragility and disintegration than the plain citrate and Moscow Institute of Hematology preservatives.

4. Marked reduction of the total leukocytes occurred with all four preservatives within 3 days, especially due to disintegration of the neutrophils, but the two carbohydrate preservatives gave somewhat better preservation than the two without dextrose or dextrin.

5. Marked reduction in the platelets occurred with all four preservatives within 3 days but both carbohydrate preservatives gave somewhat better preservation than the two without dextrose or dextrin.

6. A slight decrease in prothrombin time (Howell) was observed with the plasmas of all preserved bloods within the first 24 hours of collection of blood presumably due to disintegration of platelets. During the following 3 to 7 days this was followed by an increase presumably due to loss of prothrombin.

7. The isoagglutinins showed no decrease during the first 10 days with all four preservatives, but some diminution after 14 and 21 days which was somewhat less marked with the two carbohydrate preservatives.

8. Complement was well preserved by all four preservatives for the first 7 to 10 days.

9. The bactericidal activity of the plasmas for *B. typhosus* was well preserved by all four preservatives for 7 days following which rapid deterioration occurred.

Conclusions. Blood is better preserved by the addition of dextrose (modified Rous-Turner) or of dextrin (Maizels and Whittaker) to preservatives than by plain citrate or the Moscow Institute of Hematology methods.

Blood preserved for more than 3 days should not be used in the transfusion treatment of acute and chronic infections, the anemias and hemorrhagic states, although apparently satisfactory for the treatment of acute hemorrhage and surgical shock.*

* An additional advantage in the use of preserved blood may be greater safety from the danger of transfusion syphilis. I have inoculated 10 cc. of fresh citrated blood with 1 cc. of a heavy suspension of virulent *Treponema pallidum* (Nichols-Hough strain) from acute testicular syphilomas of rabbits showing approximately 200 treponemata per dark field. A rabbit inoculated at once with 1 cc. of the citrated blood-treponema mixture intratesticularly developed acute testicular syphilis in about 5 to 6 weeks, as likewise rabbits inoculated 1 to 3 hours later. Rabbits inoculated 1, 2, 7, 14 and 28 days later (the mixture being kept at 4° to 6° C.) escaped testicular infection and lymph gland transfers to fresh rabbits made 6 weeks later were negative. The results indicate, therefore, that *Treponema pallidum* in citrated blood may die after 24 hours of preservation at 4° to 6° C.

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VITAMIN C IN CHRONIC LEAD POISONING.

AN EXPERIMENTAL STUDY.*

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IT has been suggested that vitamins may play a rôle in heavy metal poisoning, especially with reference to the nervous system. Williams and Spies[5] are of the opinion that, while thiamin does not improve the condition of patients with chemical neuritis produced by tri-ortho-cresyl phosphate, there are theoretical grounds for believing that large doses of vitamin B_1 would act as a prophylactic.

Holmes, Campbell and Amberg[4a,b] treated several cases of chronic lead poisoning in factory workers and painters with large doses of vitamin C (100 to 200 mg. of ascorbic acid daily above the normal intake) and presented data to show that the vitamin treatment was more effective in removing the symptoms of lead poisoning and restoring the blood picture, than is the usual therapy with calcium or the institution of more adequate methods for reducing exposure hazards. They claim that those painters who normally have a high vitamin C intake do not develop lead poisoning; the vitamin acts as a detoxifying agent by forming poorly ionized, but soluble, lead compounds, and conversely that lead leaves less vitamin available for physiologic purposes. This is reflected in the lower urinary excretion levels of ascorbic acid as well as resemblance of the tooth and gingival changes of lead intoxication to subclinical scurvy.

These conclusions can be tested experimentally since guinea pigs respond somewhat like humans to both lead intoxication and vitamin C deficiency. Also, the technique for detecting vitamin C changes in the blood by measuring the complement titer as developed by Ecker, Pillemer, Wertheimer and Gradis[3] is available. Furthermore, it has been shown in this laboratory[2] that certain heavy metal salts may *in vitro* reversibly inactivate serum complement. It was also demonstrated that a direct correlation existed between the ascorbic acid content of serum and its complementary activity. Therefore it was of interest to discover whether chronic lead poisoning would lead to a weakening of complement. It is evident that the influence of lead poisoning on this relationship is worthy of further study.

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Experimental. Two experiments were conducted, one involving 46 guinea pigs and the other involving 24. The animals were placed on a diet of Purina rabbit chow which is adequate in all respects excepting vitamin C. This is present only in traces, and guinea pigs develop scurvy in 21 days on this diet. The food was not autoclaved in order to avoid destruction of other vitamins. In addition to this diet, each animal received, on alternate days, a hypodermic injection of ascorbic acid as the buffered commercial product, Cevalin, as follows:

Experiment 1.		Experiment 2.	
Mg. vitamin C.	No. animals.	Mg. vitamin C.	No. animals.
1	28	1	8
20	18	2	8
		20	8

As established in this laboratory,[1] 0.5 mg. of ascorbic acid daily is the minimum amount necessary for the well-being of guinea pigs *provided that environmental conditions are good*, while 10 mg. daily is the saturation level and represents the intake of the guinea pig in its normal habitat where it is accustomed to drastic environmental changes. The animals were stabilized for 1 month on this routine before lead was added to the diet.

Lead was administered as the basic carbonate, $2PbCO_3.Pb(OH)_2$, placed in capsules and inserted in the esophagus. The following table indicates the dose of the lead compound (80% Pb) in mg. per kg. of body weight, 2 out of 3 days for 1 month.

Experiment 1.—Dosage of Lead.

Vitamin C dosage.	Median lead dosage in mg.		Range lead dosage in mg.	
	Start.	End.	Start.	End.
0.5 mg. per day	74	95	63–88	70–108
10 mg. per day	64	69	55–73	57–78

The doses are variable due to the fact that each animal received 40 mg. of lead compound per day, and they reflect the different weights, and at the end of the experiment the loss in weight. There is sufficient overlapping in the ranges to give a complete picture, and the variations are compensated for by the variability in absorption from the intestines. However, in the second experiment the administration was maintained at 80 mg. of basic carbonate per kg. of body weight, every 2 out of 3 days for 1 month.

Results. 1. *Weight Changes.* During the period of stabilization when no lead was administered, the animals on the low vitamin intake showed variation in weight; approximately one-third gained up to 10%, an equal number lost to a similar degree, and the remainder did not change. All of the animals in the high vitamin groups gained up to 15% of the original body weight. From Table 1 it will be seen that after 1 month's administration of lead, the animals receiv-

ing the high vitamin level fared better than those on the lower intake. Of significance was the loss of 20% or more of body weight in 25% of the animals maintained on the minimal antiscorbutic level, whereas

TABLE 1.—WEIGHT CHANGES IN THE LEAD-TREATED GUINEA PIGS.

Treatment.	% loss.			% gain.		
	1–10.	11–20.	21–30	1–10.	11–20.	21–30
0.5 mg. Cevalin per day plus 40 mg. lead carbonate 2 out of every 3 days for 32 days	11	9	6	1		
Same lead dose plus 10 mg. Cevalin per day	12	2	1	2	1	
0.5 mg. Cevalin per day plus 80 mg. lead carbonate per kg., 2 out of every 3 days for 34 days	5	..	3			
Same lead dose plus 1 mg. Cevalin per day	2	2	1	2		
Same lead dose plus 10 mg. Cevalin per day	2	2	..	4		

in the animals on higher vitamin intakes this figure was approached only in isolated instances. The variations in weight changes encountered were not sufficiently great to rule out the effects of adding an offending agent to the diet of animals already on subminimal conditions for health.

2. *Changes in the Blood Picture.* In both experiments, the degree of plumbism attained, as measured by erythrocyte counts, hemoglobin estimation and number of stippled cells, was not materially different in the animals on different vitamin C intakes. The data are summarized in Table 2.

TABLE 2.—CHANGES IN THE BLOOD PICTURE OF GUINEA PIGS IN CHRONIC PLUMBISM.

Exp.	Animal.	Stabilization period.			After 1 month of lead.		
		R.B.C.*	% Hb.†	Stipple cells.‡	R.B.C.	% Hb.	Stipple cells.
		0.5 Mg. Cevalin Daily.					
1	A 5451	5.85	90	0	4.25	60	4
1	A 5425	5.20	80	0	2.90	60	6
1	A 5032	5.15	90	0	2.75	50	35
1	A 5465	4.95	90	0	3.95	60	22
2	A 5387	4.20	75	0	3.85	60	36
		1 Mg. Cevalin Daily.					
2	B 5389	5.00	75	0	3.55	60	48
2	B 5384	5.35	70	0	2.90	50	20
		10 Mg. Cevalin Daily.					
1	B 5453	5.10	90	0	3.70	65	21
1	B 4853	5.20	85	0	3.95	90	31
1	B 5404	5.05	90	0	3.30	55	14
1	B 5464	5.05	80	0	3.95	60	9
1	B 5459	5.80	100	0	3.65	60	26
1	B 5472	5.45	80	0	3.45	70	15
2	C 5380	5.35	70	0	2.30	50	52
2	C 5379	4.90	75	0	3.15	50	58

* Millions of red blood cells. † Tallqvist estimation.
‡ Number per 20 high-power fields.

3. *Changes in Complement Function and Serum Ascorbic Acid Levels.* Ecker, Pillemer, Wertheimer and Gradis[3] showed that a parallelism exists between the ascorbic acid concentration of the guinea pig serum and its complementary activity, and that the parallelism holds true until a definite level of ascorbic acid is attained at about 1 mg. per 100 cc. of serum. At this point the complementary activity reaches its maximal efficiency. In the course of this study it was also noted that this parallelism occurs even in the presence of chronic lead poisoning. The results are given in Chart 1. It will be seen that the degree of complementary activity

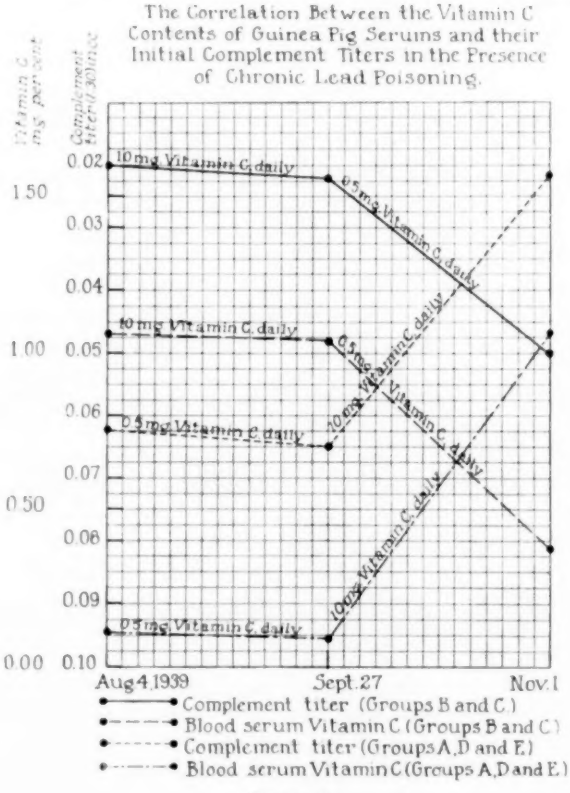

CHART 1

is dependent on the content of ascorbic acid in the serum. Holmes and his co-workers stated that the possible action of ascorbic acid in alleviating lead poisoning was the formation of a poorly ionized, but soluble, lead ascorbate complex. If this were true, it would be expected that a reduction of complementary activity as well as the blood serum ascorbic acid content would follow. However, this is not the case. The observations confirm the earlier work from this laboratory and indicate that the formation of a lead ascorbate complex does not occur.

4. *Deposition of Lead in the Organs.* The determinations of lead in the organs were made by the Kettering Laboratory of Applied Science, University of Cincinnati, Cincinnati, Ohio, and are here listed:

	No. 5379. 10 mg. vit. C/day.		No. 5392. 10 mg. vit. C/day.		No. 5381. 0.5 mg. vit. C/day.		No. 5383. 0.5 mg. vit. C/day.	
Tissue.	Mg. Pb per 100 gm.	Ratio kidney = 100.	Mg. Pb per 100 gm.	Ratio kidney = 100.	Mg. Pb per 100 gm.	Ratio kidney = 100.	Mg. Pb per 100 gm.	Ratio kidney = 100.
Kidney . .	15.0	100.0	20.0	100.0	5.0	100	23.0	100.0
Liver . . .	7.0	46.5	4.6	23.0	1.6	32	1.55	6.74
Bone . . .	7.8	52.0	16.0	80.0	10.0	200	14.4	62.6
Brain . .	0.58	3.87	0.17	0.85	0.2	4	0.25	1.1

The analytic data expressed as mg. of Pb per 100 gm. fresh tissue do not show any clear-cut effect of vitamin C on lead storage. They do suggest that the deposition of lead in the liver tends to be greater when the animal is on a saturation diet of vitamin C. The data were not sufficiently extensive to be conclusive. If the results are expressed as ratios (kidney = 100), the above mentioned effect is not so decisive. It is also worthy of note that, regardless of vitamin intake, the deposition of lead in the kidney was several times that of the liver. In acute and chronic lead poisoning in man the reverse is true.

5. *Paralysis, Convulsions and Death.* Here, the beneficial effects of a high ascorbic acid intake were striking and appear to be unequivocal. In both experiments, only 2 of the 26 guinea pigs on the high vitamin C régime developed clear-cut spasticities or paralyses, and none of the pigs died of lead poisoning during the period of observation. On the other hand, 18 of the 44 animals on the low ascorbic acid intake developed some form of neuro-plumbism and 12 died of typical lead poisoning. Of the 18 animals which developed neuro-plumbism, 4 showed signs of spasticity and clumsiness, 5 spasticity and paralysis, and 9 developed convulsions.

6. *Vitamin C as a Therapeutic Agent in Lead Poisoning.* When 15 of the animals originally on 0.5 mg. Cevalin daily had received lead for 1 month, and were in frank plumbism, they were taken off the lead diet, and 7 of these were retained on the low vitamin level and 8 were raised to the daily 10 mg. Cevalin level. Both groups showed a rapid weight gain, increase in erythrocyte count, and disappearance of stippled cells. The degree of recovery in 1 month was not strikingly greater in the high vitamin group as compared to the lower vitamin group. In contrast to its prophylactic action, ascorbic acid failed to show any beneficial effect on the spasticities and paralyses. The results are shown below:

WEIGHT CHANGES IN POISONED GUINEA PIGS TAKEN OFF LEAD.

Continued on 0.5 mg. Cevalin daily.		Raised to 10 mg. Cevalin daily.	
% stabilized weight restored.	No. animals.	% stabilized weight restored.	No. animals.
90–100	3	74	1
100–110	2	90–100	2
127	1	100–110	4
		117	1

BLOOD PICTURE UNDER SIMILAR CONDITIONS.

% increased R.B.C.	% increased Hb.	Stippled cells.	% increased R.B.C.	% increased Hb.	Stippled cells.
10	25	0	40	16	0
24	20	0	60	50	0

Summary and Conclusions. 1. In two series of 44 guinea pigs on a subclinical scurvy intake of vitamin C, the degree of lead poisoning developed in 1 month by oral ingestion of basic lead carbonate was more severe when compared to the plumbism in two groups of 24 pigs on a saturation level of the vitamin.

2. The vitamin was not significantly protective against weight loss, anemia and stippling.

3. The vitamin was effective in preventing the onset of neuroplumbism.

4. No evidence has been found to show that lead has any effect on vitamin C utilization or its metabolism.

5. As a therapeutic procedure, vitamin C is inefficient as compared to removal of exposure to lead.

6. Complementary activity of the serum of the animals in lead poisoning was parallel to the ascorbic acid concentration of the serum, and was not influenced by the lead intake.

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THE PLASMA COAGULATION TIME AS A SIMPLE TEST FOR VITAMIN K DEFICIENCY.*

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VITAMIN K deficiency in chicks causes a hemorrhagic diathesis characterized by a diminution in the amount of thermolabile blood globulins (prothrombin) associated with prolonged blood and plasma coagulation times, and traumatic and spontaneous hemorrhages. It is now evident that a similar hemorrhagic tendency may

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develop in humans in certain cases of hepatitis, obstructive jaundice,[9] the hemorrhagic diathesis of the new born,[10] and in a few other disorders[1b,2,13] due to vitamin K deficiency. Consequently, a simple clinical test for a deficiency of this vitamin is highly desirable. Quick's test of prothrombin time[5] and that of Ziffren and his coworker at Iowa[12] were devised for this purpose, but they present certain technical difficulties which limit their use. Howell's test of prothrombin time has met with a number of objections, chief of which are that it does not measure prothrombin and that it varies with the concentration of platelets present in the blood plasma, the time and speed of centrifugation, the temperature, the quantity of calcium added, and certain other variables.

As this report is concerned with the technique and serviceability of a simple clinical test to determine the desirability of administering vitamin K therapeutically, the theories of blood coagulation[3] and their relationship to the recently discovered vitamin[8] need not be reviewed again. The proposed test of blood plasma coagulation time is a modification of Howell's test of prothrombin time. It is based on the fact that the recalcified plasma of oxalated normal blood will usually coagulate in a given length of time and that in hemophilia and in pronounced cases of vitamin K deficiency the time is considerably longer than normal. The many factors which influence the test but slightly become relatively unimportant in the procedure as outlined, as the test has shown a consistent uniformity under normal conditions and a definite departure from normal in certain hemorrhagic diatheses.

It has been carried out 125 times on the blood of 100 normal individuals and 110 times on 59 patients with disorders unrelated to hemorrhagic conditions and deficiency states; and 64 times on normal chickens. It has also been carried out 105 times on 40 cases of biliary tract disease, some of which have already been reported,[1b,6] on patients with hemophilia and purpura, and on 85 chicks in various stages of vitamin K deficiency.

Technique. Whole blood is obtained by a clean venepuncture and added to a previously oxalated centrifuge tube. The standard amount of oxalate used is 10 mg. per 5 cc. of blood, using the dry potassium salt. A number of tubes containing sufficient oxalate for 2, 5, or 10 cc. of blood may be prepared in advance. The oxalated blood is then centrifuged for 5 minutes at 3500 revolutions per minute in a constant speed Gyro centrifuge.[7] The clear plasma is then pipetted off. Four small chemically clean test tubes, $\frac{3}{8}$ inch in diameter, are then set up with varying amounts of 0.4% calcium chloride solution. The first tube contains 0.5 cc. (2 mg. calcium chloride); the second 0.4 cc. (1.6 mg. calcium chloride); the third 0.2 cc. (0.8 mg. calcium chloride); and the fourth 0.1 cc. (0.4 mg. calcium chloride). Two-tenths centimeters of the plasma to be tested is added to each of the tubes and they are shaken briskly about 10 times without corking or inverting. The time that a firm clot forms in each tube (will not flow when tube is held horizontally) is noted, and the length of time recorded from the mixing

of the plasma and calcium chloride to the time of clot formation is the plasma coagulation time for each of the 4 calcium chloride dilutions. The shortest time recorded is the coagulation time of the plasma, while the longest time recorded is the plasma coagulation time with an excess of calcium which is 2 to 5 times the optimum amount.

The use of 10 mg. of dry potassium oxalate per 5 cc. of blood was selected because this amount of oxalate is in general use already.[11] A high speed centrifuge was chosen with a time limit of 5 minutes because such a centrifuge has already been utilized for blood studies by Rytand[7] and does away with irregularities in speed and time. Centrifuging the blood more slowly over a longer period of time will apparently give comparable results.

In the Quick technique for determining prothrombin times, solutions of oxalate and calcium chloride are used which permit an excess of calcium to be added which makes the results inconsistent and usually produces a prolonged time because of an excess of calcium.[4] In developing the technique of the present test, a standard amount of oxalate per cm. of blood was selected and varying amounts of calcium added to the plasma in order to determine the exact range where optimum calcification occurred to produce the shortest clotting time.

In conducting these studies 3 sets of 10 tubes each were set up, each series containing diminishing amounts of 0.4% calcium chloride as follows: 1.0 cc., 0.9 cc., 0.8 cc., 0.7 cc., 0.6. cc., 0.5 cc., 0.4 cc., 0.3 cc., 0.2 cc., and 0.1 cc. To each tube was added 0.2 cc. of plasma; blood from 3 different patients being used for each series. It was noted that clotting was most rapid in the second half of the tubes and that the differences from tube to tube in the second half tended to be very slight. In setting up a similar series of 6 tubes containing the following amount of calcium, 2 mg., 1.6 mg., 1.2 mg., 0.8 mg., 0.4 mg., and 0.2 mg., the most rapid clot formation nearly always occurred in the fourth (0.8 mg.), or the fifth (0.4 mg.) tube. Out of 45 such studies, the most rapid clotting occurred 17 times in the 0.4 tube, 17 in the 0.8; in 10 it was the same in both tubes, and it occurred once in the 1.2 mg. tube. These optimum times never occurred in the 2 mg., the 1.6 mg., or the 0.2 mg. tubes. Coagulation occurred in the last tube only once and did not occur in the 0.4 mg. tube on 8 occasions. The longest time usually occurred in the first tube but the times for the first and second tube were often identical or very nearly the same. Consequently, in setting up routine tests, the 2 mg., 1.6 mg., 0.8 mg., and 0.4 mg. tubes only were retained. In 100 tests using 4 tubes, the most rapid clotting occurred in the third tube in 38%, in the fourth tube in 29%, and was the same in the third and fourth tubes in 33%. No clotting at all took place in the fourth tube in 11% of the tests. The first and second tubes are of no additional value in normal tests; but when the plasma coagulation time tends to be prolonged, the tendency is often much more pronounced when an excessive amount of calcium is present than in the tubes containing an optimum amount of calcium.[1b] A number of tubes containing the four solutions of 0.4% calcium chloride (0.5 cc., 0.4 cc., 0.2 cc., and 0.1 cc.) may be made up at a time, stoppered, and put away for future use. Dry calcium chloride tends to cause irregular results apparently because of improper mixing with the plasma.

All tests have been run at room temperature which has varied between 68 and 80° F. The higher temperatures tend to produce slightly more rapid coagulation, but serial tests on the same patient on 5 different days with a variation in laboratory temperature of 12° F. did not alter the coagulation time more than 1 minute above or below the average reading.

Preferably the test should be carried out within 30 minutes after the blood has been drawn, as the rapidity of plasma coagulation tends to diminish after standing 1 or more hours at room temperature. However, in testing the stability of plasma coagulation in 41 normal patients 2 hours after the

blood was drawn, it was found that the time was not increased over the initial reading in 13 (31.7%) and was still within normal limits in 18 (43.9%) more. In 7 of the remaining 10 it was only 9, 1 minute above the normal limit. In the other 3 it was 10, 12, and 13 minutes respectively. When it was retested in 23 patients after 4 hours, it was not increased in 6; was still within normal limits in 7 more; and ranged between 9 and 20 minutes in the 10 remaining plasmas. When the plasma coagulation time is longer than normal, the tendency to prolongation on standing at room temperature is more pronounced. It is also more pronounced in the tubes containing an excess of calcium.

The accuracy of the test is well shown by studying the plasma coagulation time on separate specimens of blood taken at hourly intervals. This was done coincident with a standard glucose tolerance test on 3 individuals. The results are shown in Table 1. The variation in the times was only 1 to 2 minutes when an optimum amount of calcium was used and only 2 to 3 when an excess was used.

TABLE 1.—PLASMA COAGULATION TIMES ON SPECIMENS OF BLOOD TAKEN HOURLY DURING A GLUCOSE TOLERANCE TEST. ONLY SLIGHT VARIATIONS OCCUR. COAGULATION TIME IN MINUTES.

Case.	Amount of Ca.	1st hr.	2d hr.	3d hr.	4th hr.	5th hr.	Variation.
F. A. . . .	Optimum	5	6	6	7	..	2
	Excess	7	9	10	9	..	3
J. B. . . .	Optimum	6	6	6	7	6	1
	Excess	7	7	7	9	7	2
M. F. . . .	Optimum	7	9	7	8	..	2
	Excess	11	12	13	12	..	2

Only 0.8 cc. of blood plasma is required for the test. This amount is readily obtained from 2.5 cc. of whole blood. If less blood is available, the test can be carried out with 0.4 cc. of plasma by adding 0.1 cc. of plasma to each of the 4 tubes which contain only one-half the usual amount of 0.4% calcium chloride (0.25 cc., 0.2 cc., 0.1 cc., and 0.05 cc.). Occasionally homogeneous, firm clots do not form, but a small pellicle becomes solid or a partial web-like clot occurs. In such instances which are most likely to take place when the coagulation time is prolonged, the end point should be read at the time a firm clot forms whether or not the whole solution is involved. The exact cause of such partial clotting is not known.

Ordinarily the whole technical procedure from the time of drawing the blood to setting up the 4 tubes to read the coagulation time takes on the average about 8 minutes. The method has the advantage of requiring only 2 stable solutions (2.0% potassium oxalate and 0.4% calcium chloride). No unstable tissue extracts need be added, and no constant temperature water bath is required.

Results of Plasma Coagulation Time Tests in 100 Normal Subjects. The test was carried out on 13 normal medical students, 18 normal student nurses, and on 69 patients without evidence of organic disease. (See Table 2 and Chart 1.) Their ages varied between 16 and 60. There were 38 males and 62 females. The average normal plasma coagulation time was found to be 5.38 minutes, varying between 2 and 8 minutes when an optimum of calcium is added. When an excessive amount of calcium is added, the average normal time was found to be 8.61 minutes with the limits of variation lying between 3 and 15

minutes. The blood coagulation times for the same group of normal individuals is also shown in Table 2. The average time is 5.27 minutes, with the limits of variation lying between 3 and 11.

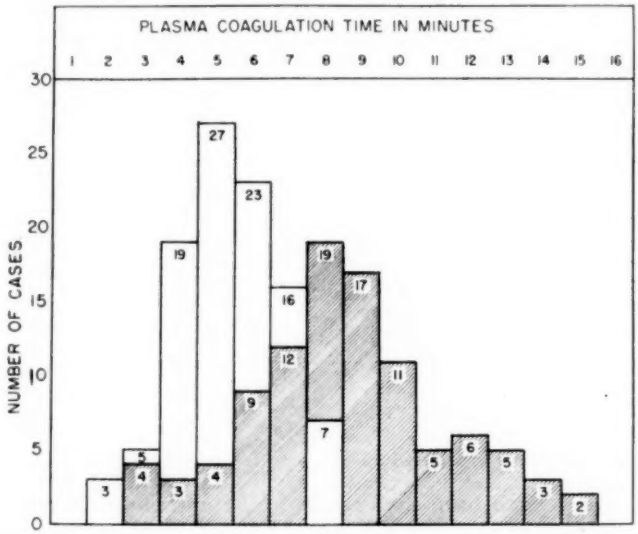

CHART 1.—Distribution of normal plasma coagulation times in 100 individuals. White blocks = coagulation time with optimum amount of calcium; cross-hatched blocks = coagulation time with excess of calcium.

Results of Plasma Coagulation Time Tests in 149 Chicks. Vitamin K deficient chicks were raised in the laboratory as previously described.[15] The study of normal chicks was of necessity confined to birds on a similar diet receiving adequate amounts of vitamin K, usually as a supplement of alfalfa to the diet. Blood studies were

TABLE 2.—BLOOD AND PLASMA COAGULATION TIMES; DISTRIBUTION OF 100 NORMAL CASES BY INCIDENCE PER NUMBER OF MINUTES.

	Coagulation time in minutes.															
Number . . .	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Av.
Blood	0	0	8	33	30	9	8	5	1	4	2	0	0	0	0	5.27
Plasma with optimum Ca. . . .	0	3	5	19	27	23	16	7	0	0	0	0	0	0	0	5.38
Plasma with excess Ca.	0	0	4	3	4	9	12	19	17	10	5	6	5	3	2	8.61

carried out on chicks which were usually 3 and 4 weeks of age but occasionally older chicks were used. Normal blood coagulation time was taken as 1 to 10 minutes, as previously noted[1,8] but with variation up to 30 minutes in a few rare instances. No opportunity has been offered to study the plasma coagulation time of chicks on the range. Consequently, those chicks with an adequate diet and

a normal blood coagulation time have been considered normal as far as their plasma coagulation was concerned. Table 3 presents the results of these studies in 64 normal chicks, and Table 4 shows the results of similar tests in 85 fowls with vitamin K deficiency.

TABLE 3.—THE BLOOD AND PLASMA COAGULATION TIMES IN 64 NORMAL CHICKS ON A DIET ADEQUATE IN VITAMIN K. COAGULATION TIMES IN MINUTES.

Blood.	Plasma.	Blood.	Plasma.	Blood.	Plasma.	Blood.	Plasma.
½	(c)*	2	(c)*	2	9	4	3
½	5	2	2	2	9	4	4
1	(c)*	2	3	2	10	4	7
1	(c)*	2	3	2	10	4	9
1	1	2	5	2	12	4	9
1	1	2	5	2	13	4	10
1	2	2	5	2	13	5	1
1	2	2	5	2½	8	5	1
1	2	2	5	3	(c)*	5	5
1	6	2	5	3	2	5	6
1½	2	2	5	3	7	5	8
2	(c)*	2	6	3	7	5	9
2	(c)*	2	6	3	8	5	11
2	(c)*	2	6	4	(c)*	5	15
2	(c)*	2	6	4	(c)	6	4
2	(c)*	2	8	4	1*	6	10

* Blood coagulated in oxalated tube.

The birds have been divided into four groups according to the length of time it took their blood and plasma to coagulate. Group 1 includes 20 birds in which the deficiency seemed doubtful or borderline. These birds were on a deficient diet but their blood coagulation times were within normal limits although greater than the normal average. None of the plasma coagulation times was over 30 minutes in the group. Group 2 is composed of 30 birds with a moderate deficiency. The blood coagulation times were longer than the average in all but 2 instances, but all were still within the normal limit of variation. However, all the plasma coagulation times were moderately to greatly prolonged. Group 3 consists of 17 birds with marked vitamin K deficiency showing prolonged blood and plasma coagulation times. Group 4 is composed of 8 birds with a total deficiency. The blood and plasma showed no tendency to coagulation in 10 to 48 hours of observation. The last three groups with the prolonged times showed the usual tendency to both spontaneous and traumatic hemorrhages, the tendency increasing with each group. The times found in Groups 1 and 2 and more rarely in 3 correspond to similar studies in vitamin K deficient patients.

Serial studies of the blood and plasma coagulation times were carried out in a number of birds receiving vitamin K therapy. Four deficient birds were tested and placed on a dietary supplement of 25% alfalfa and the coagulation times followed over a period of 30 days. All the birds showed similar results. The findings in 2 are charted in Chart 2 and show the reduction in blood and plasma coagulation times to normal. In a similar group of 3 birds a single

TABLE 4.—BLOOD AND PLASMA COAGULATION TIMES IN 85 CHICKS WITH VARYING DEGREES OF VITAMIN K DEFICIENCY.*

Doubtful deficiency.		Moderate deficiency		Marked deficiency.		Total deficiency.	
Blood.	Plasma.	Blood.	Plasma.	Blood.	Plasma.	Blood.	Plasma.
7 min.	2 min.	1½ min.	35 min.	30 min.	> 7 hrs.	>10 hrs.	>10 hrs.
7 "	7 "	4 "	56 "	33 "	>48 "	>24 "	>24 "
7 "	9 "	5 "	1 hr. 27 min.	34 "	>24 "	>24 "	>24 "
7 "	13 "	8 "	43 min.	40 "	1 hr. 29 min.	>24 "	>24 "
7 "	22 "	8 "	>12 hrs.	42 "	43 min.	>24 "	>24 "
8 "	11 "	9 "	1 hr. 32 min.	42 "	>48 hrs.	>48 "	>48 "
8 "	24 "	10 "	31 min.	60 "	>12 "	>48 "	>48 "
9 "	16 "	11 "	40 "	60 "	>24 "	>48 "	>48 "
10 "	24 "	11 "	1 hr. 31 min.	1 hr. 1 min.	>48 "		
12 "	25 "	11 "	>24 hrs.	1 hr. 2 min.	24 "		
12½ "	20 "	12 "	31 min.	1 hr. 3 min.	>24 "		
12½ "	21 "	12 "	36 "	1 hr. 12 min.	1 hr. 22 min.		
13 "	14 "	12 "	36 "	1 hr. 13 min.	2 hrs. 12 min.		
13 "	20 "	12 "	54 "	1 hr. 18 min.	2 hrs.		
14 "	16 "	12½ "	36 "	1 hr. 25 min.	2 hrs. 28 min.		
17 "	23 "	13 "	>60 hrs.	7 hrs.	>48 hrs.		
19 "	23 "	15 "	>12 "	48 "	>48 "		
20 "	9 "	15 "	>24 "				
20 "	22 "	16 "	> 4 "				
23 "	11 "	17 "	5 hrs. 53 min.				
		18 "	1 hr. 13 min.				
		18 "	> 3 hrs.				
		18 "	> 4 "				
		19 "	53 "				
		21 "	>48 "				
		24 "	>48 "				
		26 "	>48 "				
		27 "	31 min.				
		27 "	2 hrs. 29 min.				
		29 "	>24 hrs.				

* Many birds in the last two groups bled to death.

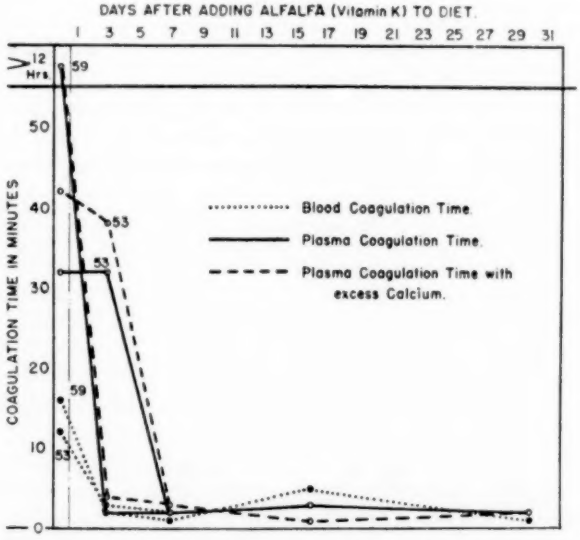

CHART 2.—Reduction in blood and plasma coagulation times to normal on adding alfalfa to the diet of 2 vitamin K deficient chicks (No. 53 and No. 59).

dose of 1 mg. of vitamin K orally reduced the times to normal overnight. Subsequently the birds were kept on a vitamin K deficient diet only. Gradual prolongation of the coagulation times occurred

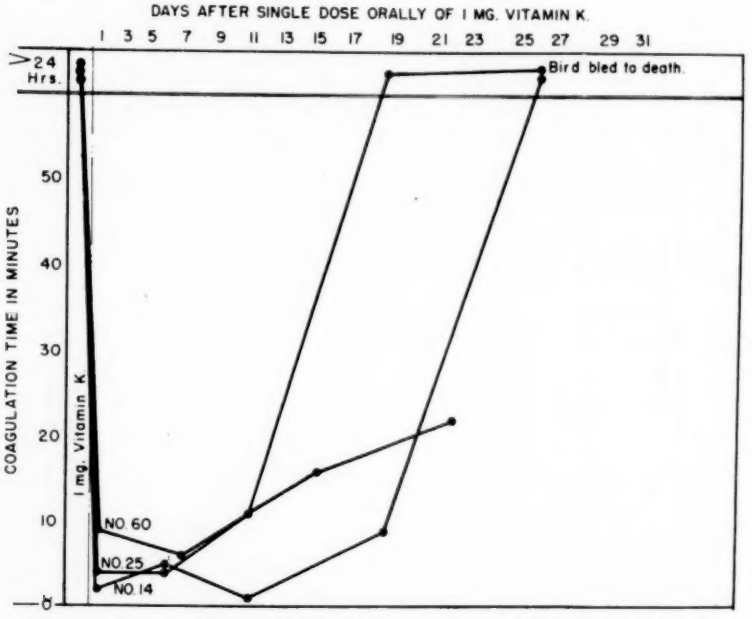

CHART 3.—Effect of a single dose of vitamin K on the plasma coagulation times of 3 chicks fed on a vitamin K deficient diet. Rapid fall to normal with gradual prolongation after the first 11 days. Failure of coagulation in 2 birds on the 26th day with fatal hemorrhage in 1.

in all three birds, resulting in death from hemorrhage in one as shown in Chart 3. A group of 6 birds was similarly treated with a single dose of 2 mg. of synthetic vitamin K (2-methyl-1-4 naphthoquinone).

TABLE 5.—REDUCTION OF BOTH BLOOD AND PLASMA COAGULATION TIMES TO NORMAL IN 3 VITAMIN K DEFICIENT CHICKS 24 HOURS AFTER A SINGLE INTRAMUSCULAR INJECTION OF 2 MG. SYNTHETIC VITAMIN K. PERSISTENCE OF NORMAL TIMES FOR 9 DAYS SHOWN IN 2 BIRDS.

Bird No.			Coagulation time before injection of vitamin K.	Coagulation time after injection of vitamin K. 24 hrs.	9 days.
39		Blood	15 min.	1 min.	2 min.
	Plasma	Optimum Ca.	>24 hrs.	1 "	2 "
		Excess Ca.	>24 "	2 "	3 "
62		Blood	11 min.	1 min.	1 min.
	Plasma	Optimum Ca.	1 hr. 31 min.	2 "	2 "
		Excess Ca.	1 " 38 "	3 "	3 "
69		Blood	12 min.	½ min.	
	Plasma	Optimum Ca.	25 "	½ "	
		Excess Ca.	1 hr. 3 min.	2 "	

They all responded rapidly within 40 to 60 minutes. The blood changes in 1 are recorded graphically in Chart 4*A*. Synthetic vit-

amin K in 2 mg. doses (4-amino-2-methyl-napthol hydrochloride)* was injected intramuscularly into 3 birds with vitamin K deficiency. As shown in Table 5 all showed a reduction to normal coagulation times by the next day, and 2 were still normal nine days later, despite the continuation of the deficient diet. Similar intramuscular injections in 1 mg. doses were given to 12 birds. The blood and plasma coagulation times were very rapidly reduced, usually within 20 to 30 minutes, reaching normal well within an hour. A typical example is given in Chart 4*B*.

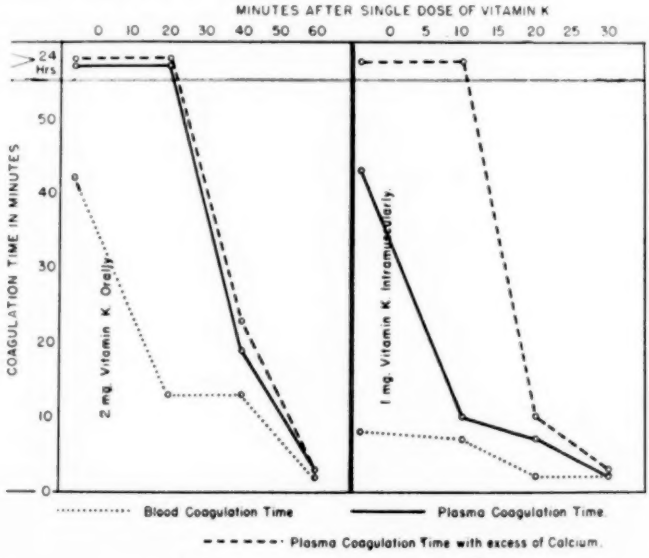

CHART 4.—Effect of single large dose of synthetic vitamin K on the blood and plasma coagulation times in vitamin K deficient chicks. Normal within 60 minutes after administration by mouth in *A* and within 30 minutes after injection in *B*.

The results of the plasma coagulation time studies in these chicks, particularly when serial tests were carried out relative to vitamin K administration, show the test to be highly satisfactory in following experimentally controlled vitamin K deficiency and tend to substantiate the results of the tests obtained in normal and vitamin K deficient humans.

Vitamin K Deficiency in Man. The plasma coagulation time has been studied in 40 cases of liver and biliary tract disease in man. The test has proven just as satisfactory as in the studies with chicks. Three case studies have already been reported showing pronounced deficiency and return to normal findings coincident with the administration of vitamin K preparations.[1b,6] The effect of vitamin K therapy in patients with obstructive jaundice is well illustrated

* Supplied by Parke-Davis & Co.

in Chart 5. The relationship of the plasma coagulation time to treatment is shown in a patient with a slight deficiency, a patient with a moderate deficiency, and a patient with a marked deficiency complicated by hemorrhage. The improvement in plasma coagulation is consistent in each instance and the charts are very similar to those shown for chicks.

The plasma coagulation time was studied in 10 patients with thrombocytopenic purpura. All were found to be within normal limits despite the presence of active bleeding in several.

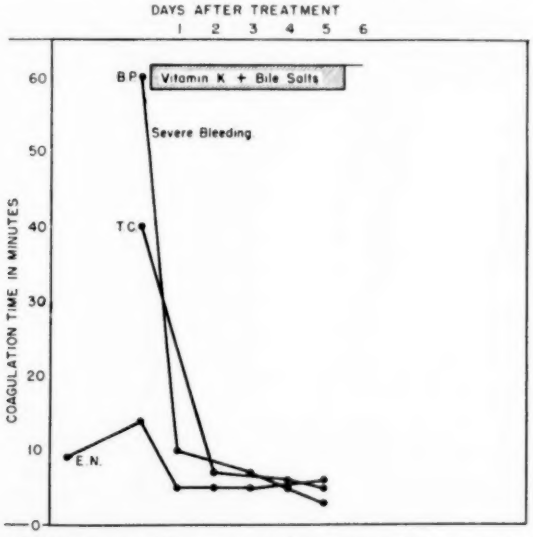

CHART 5.—Reduction of plasma coagulation times in 3 patients with obstructive jaundice coincident with vitamin K and bile salt therapy. The cases represent different degrees of deficiency. All became normal by the second day.

Summary. 1. A technique for measuring the plasma coagulation time of recalcified oxalated blood plasma has been outlined which is a modification of Howell's measurement of prothrombin time.

2. The technique of the test is simple to carry out and gives results which are sufficiently constant to be reliable for clinical use. No unstable tissue extracts are required.

3. Normal standards of plasma coagulation time have been obtained based on a study of the blood of 100 normal individuals.

4. The suitability of the plasma coagulation time as a test for vitamin K deficiency has been shown in a study of the blood of 149 chicks, 85 of which were vitamin K deficient.

5. The test has proven satisfactory in the diagnosis and treatment of jaundiced patients with vitamin K deficiency.

The writer is indebted to Miss Thelma Olsen and Mrs. Nellie Lee for their technical assistance; and to The Poehlmann Hatchery in Petaluma, Calif., for supplying all the birds studied.

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A QRS PATTERN OF DIAGNOSTIC VALUE IN THE ELECTROCARDIOGRAM

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There is a continually increasing number of reports on electrocardiographic changes described as diagnostic or characteristic of the various types of heart disease. To be of value in the interpretation of clinical records, such changes must occur in tracings from diseased hearts and at the same time be absent, or extremely rare, in those obtained from normal hearts. Likewise, the greater the frequency of changes in electrocardiographic records from diseased hearts, particularly in the absence of accepted electrocardiographic evidence of heart disease, the more important they become in diagnosis. The changes in the *QRS* complex about to be described, we believe, answer these requirements and justify a report.

The characteristics of the curves under consideration may be seen by inspection of the examples given in Chart 1. It can be noted that the *QRS* complex in Lead I is directed chiefly upward, while in Lead III it is directed chiefly downward. These changes are characteristic of left axis deviation. However, inspection of the *QRS* group in Lead II shows that, unlike the usual curve of left axis deviation, R_2 is greater than R_1. S_3 is decidedly out of phase with R_2, occurring later. The first portion of the *QRS* group, if plotted on Einthoven's triangle, shows directional components in the range of so-called normal axis deviation (+90 to +30 degrees),

whereas the latter portion of the *QRS* group shows an unusual rotation of the directional component counterclockwise into the range usually called left axis deviation.

To determine the possible significance of such curves, search was made in the files of the Heart Station of The Charity Hospital for all electrocardiograms which displayed a major upward deflection in Lead I, a major downward deflection in Lead III, and R_2 greater than R_1. Curves were selected only when the *QRS* time intervals were in normal range (less than 0.1 sec.) and when S_3 was 6 mm., or greater, with proper standardization. The reasons for discarding curves with the amplitude of S_3 less than this arbitrary level will become evident below. In 19,000 curves, 61 (0.32%) satisfied the criteria laid down. In every instance the axis index was within normal range. This is in the range of frequency of such conditions

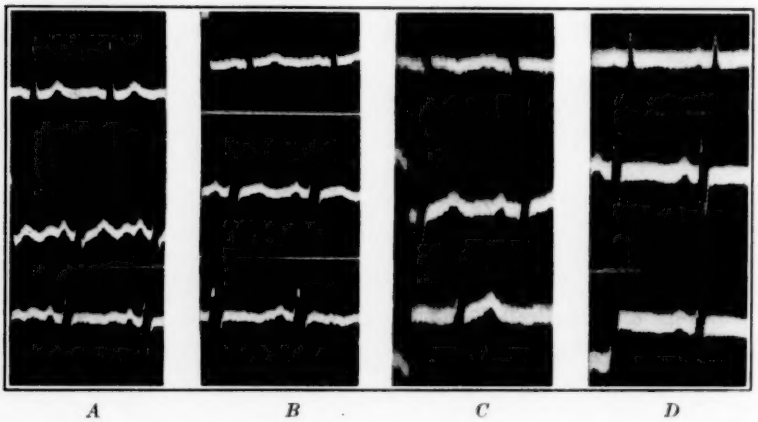

CHART 1.—Examples of the *QRS* pattern described in the text. *A*, *B*, and *C* with "high" R_1, *D* with "low" R_1.

as ventricular paroxysmal tachycardia and complete auriculoventricular heart block. In 57, there were sufficient data to establish the presence or absence of heart disease. Of these, 54 (94.7%) were known definitely to have heart disease.

These tracings were then classified in three ways: 1, according to the height of R_1; 2, according to the presence or absence of other electrocardiographic evidences of heart disease (such as inverted T_1); and 3, according to diagnosis, to elicit the possible causes of the changes. In the first group division was made into curves with R_1 greater than 5 mm., and those with R_1 5 mm. or less (Chart 1). It was found that in the group with low R_1 the percentage of diseased hearts was 83.3. With the taller R_1, all but one (97.7%) showed definite heart disease. The second grouping, according to the presence or absence of other electrocardiographic evidences of

heart disease, indicated that a significant percentage (59%) of such *QRS* changes occurred when no other electrocardiographic evidence of myocardial disease was present. Of these, 90.6% had definite evidence of heart disease, and when the patients showing high complexes in Lead I and normal *T* waves are considered, 95% had definite heart disease. The third grouping, according to diagnosis, showed that almost invariably curves of this type occurred in patients with types of heart disease that produced strain upon the left ventricle. In the group with tall R_1, 36 of the 45 patients with adequate data for diagnosis had either arteriosclerotic or hypertensive heart disease, or both. Six had syphilitic heart disease, 1 rheumatic heart disease, 1 beriberi, and 1 severe anemia. With low R_1, there were 4 patients with arteriosclerotic and hypertensive heart disease, 3 with syphilitic heart disease, 2 with rheumatic heart disease, 1 with toxic myocarditis and definite *T* wave changes, and 2 with no heart disease.

Discussion. As stated above, casual inspection of the tracings in Chart 1 leads to discovery of changes which set them apart from ordinary left axis deviation. R_2 is greater than R_1 and S_3 occurs late in relationship to these two waves. The first portions of the curves corresponding to R_1 and R_2 show an axis between +30 and +90 degrees which rotates markedly near the end of the *QRS* complex to a negative value. This rotation of the electrical axis sets these curves apart both from normal and from usual left axis deviation. The problem arises as to when this rotation becomes abnormal. In practical terms, it involves the determination of when, under these circumstances, the magnitude of S_3 becomes abnormal. If one covers most of the S_3 of Chart 1*A*, then the remainder of the curve in view in all three leads appears normal. If then one exposes more and more of S_3, when will one state that the curve is abnormal? Such a criterion would depend, as stated in the introduction to this paper, upon the height and frequency of S_3 when R_2 exceeds R_1 in the electrocardiograms of normal individuals.

Search of the literature on these points reveals little information of value. Values for S_3 reported in the literature by Lewis,[3] Wilson,[5] Chamberlain and Hay,[1] and Jensen, Smith and Cartwright[2] for normal individuals from the first to the seventh decade of life, vary from 0 to 13 mm. Included in all these groups, however, are tracings of the usual type of left axis deviation with R_2 smaller than R_1. We have been unable to find in the literature any values for curves of the type we are reporting. In Wilson's report on 104 normal individuals, elimination of the tracing with an S_3 of 13 mm., known to be a curve with typical left axis deviation, reduced the maximum value for S_3 to 4.5 mm. Lewis in 52 healthy subjects found a maximum S_3 of 4 mm.; axis deviation was not stated. In the 19,000 tracings from which the present group was taken, only 3 (0.015%), with an S_3 of 6 mm. or more were known to be normal. From 0 to

5 mm. there were many tracings from normal individuals, all of which were discarded. From these data, 6 mm. appears to be the borderline of normal limits, although we cannot say that an occasional or rare normal individual will not exceed it. However, such examples have not been found by us in the literature.

The establishment of such criteria, although the borderline may be indecisive, permits further interpretation of our tracings with abnormal T waves. Since such T wave changes stamp the curve as abnormal in any case, the establishment of such QRS changes in the absence of other electrocardiographic evidence of heart disease is important in their evaluation as a sign of heart disease. The absence of these changes in normal hearts is also necessary. Since the data support such findings, one can assume that the QRS changes are further evidence to support the T wave abnormalities. The frequent occurrence together of inverted T_1 and the QRS changes would be expected from the correlation of the latter with the diagnosis. T_1 inversion, as a sign of myocardial disease, is characteristic of left ventricular lesions, and the diagnosis in the presence of the QRS changes herein reported, whether in association with T_1 inversion or not, is almost invariably one affecting the left ventricle.

Deep S_2 and S_3 in left ventricular disease, as well as T_1 inversion, are changes known to result from anterior myocardial infarction. In such instances, R_1 often becomes diminished in size. Two instances of myocardial infarction are included in the present group. Inspection of many curves of anterior myocardial infarction from the literature indicates that the QRS relationships here stressed sometimes occur in this condition.

Whereas the curves of anterior myocardial infarction falling into the present group have been accompanied by T wave changes, there is another similar group with normal T waves which deserves mention. These are patients of asthenic habitus, without organic heart disease, who display, instead of a tendency toward right axis deviation with low R_1, a left axis deviation with low R_1. Two such patients have been reported by one of us.[4] In these, R_2 equalled R_1 in one and exceeded it in the other. We have studied the curves of some others, while eliminating tracings which fell short of the criteria for the present study. Although such findings, unlike the tendency to right axis deviation, are not common with the ptotic heart, they do occur, apparently as the result of unusual rotation or peculiarities of Purkinje architecture, and indicate that the only consistent electrocardiographic finding in ptotic heart is a low R_1. Two of the patients in the presently reported group appear to fall in this category, with R_2 greater than R_1, and account for our division of the cases into a "low" R_1 and "high" R_1 group. Elimination of such patients is necessary before the criteria given can be used in the "low" R_1 group as diagnostic of myocardial changes.

Conclusion. A *QRS* pattern is described which has been found to occur in tracings from patients with heart disease in the absence of any other electrocardiographic evidence of heart disease. It promises to be of value in electrocardiographic interpretation.

We wish to thank Dr. Richard Asfiman, Director of the Heart Station, Charity Hospital of Louisiana, for the privilege of using the records analyzed.

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THE VASCULAR "SPIDER" ASSOCIATED WITH CIRRHOSIS OF THE LIVER.

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The vascular "spider" (nævus araneus; spider telangiectasis; spider angioma) is a bright red lesion, characterized by a central point from which radiate fine, hairlike branches for a distance of about 1 cm. Because of this configuration it also has been called stellate nævus (étoile vasculaire). The central point, or core, is generally of pinhead size and is barely palpable. However, larger centers, from one to several millimeters in diameter, may be distinctly elevated. Vascular spiders are seen usually on the skin of the face, arms, fingers, and upper trunk, and only occasionally on the lower trunk and legs. At times they appear to favor sites of previous injury to the skin, as from furuncles or puncture wounds. They also occur in mucous membranes of the nasal septum, lips, tongue, conjunctivæ, and less often of the gastro-intestinal or genito-urinary tracts. Lesions in the mucous membranes are prone to bleed. Our interest in the spider was aroused by its high incidence in liver disease and by the occurrence of three spurting hemorrhages arising from these tiny spots—one on the lip, one on the arm, and one on the thorax—none of which was of a size large enough to suggest the rare pulsating angioma described in the literature.

The occurrence of a congenital form (hereditary multiple telangiectases or angiomatosis; Rendu-Osler disease) was established by the studies of Rendu[24] and of Osler.[22] Their observations have received confirmation in many subsequent case reports.[10,25]

In 1890 Hanot[15] observed their frequent association with liver disease. Osler,[22] Bouchard,[4] Gilbert and Herscher,[8] and others have also noted this coincidence. However, no data are available on the actual incidence of these lesions in persons with liver disease. Of 63 patients with cirrhosis of the liver, studied by us, 48 exhibited these structures. It is not unusual to see fresh lesions appear while others disappear in the course of the disease. Fiessinger[6] expressed the opinion that they were of prognostic significance, since they disappeared in certain patients who made clinical recovery. Bloomfield[2] described one such instance.

There are uncertainties as to the nature of the vascular spider. It is not clear from the literature on this subject whether the structure is on the arterial or venous side of the vascular tree, or whether it represents a dilatation or a new growth of vessels. These lesions have been described simply as vascular channels,[1,9,14] as venous dilatations,[3,22] and as arterial nævi or angiomata.[8,17,19] In other reports, a larger pulsating form has been described as a rare and peculiar type of lesion.[28–30]

It is noteworthy that Gilbert and Herscher in 1903 observed pulsations in these lesions, and on this account they considered them to be arterial angiomata. Steinmann[26] observed that they faded when pressure was applied to the central point. Fiessinger[6] concurred in these findings. The present report confirms the latter observations. In addition to studies on the direction of flow within the vessels and on pulsations, these structures have been examined with regard to intravascular pressure, contractility, reaction to drugs, and histologic characteristics.

Observations. *Direction of Flow.* When a point of pressure is applied to the central core of the spider, the smaller branching bloodvessels empty. Pressure applied at the periphery does not influence the central point. The flow, therefore, is directed from the center towards the periphery.

Pulsation. It is possible, even on palpation of the very small spiders, to feel a definite, though feeble, pulsation. The application of a cover glass over a spider with sufficient pressure produces regularly a rhythmic flush and pallor that synchronizes with the subject's radial pulse.

In order to quantitate the pulsation, a procedure was devised by which a magnified image of the vessel excursion could be observed. A mirror, about 1 mm. square, was fixed to the spider by collodion or egg white. A control mirror was fixed to an adjacent area of the skin, about 1 cm. distant. In a dark room, a beam of light was directed at the mirrors, which reflected magnified images on the

ceiling. In the case of spiders on the wrist or fingers a frank pulsation arose from the mirrors adfixed to the vessels, but none from the controls. However, when mirrors were located on the trunk or near a large artery, the controls likewise pulsated, due (it seemed) to vibrations transmitted from nearby arteries.

Pressure Within the Spider. One patient exhibited several typical spiders on the forearm, which were selected for study. On elevating the arm above the head, the superficial arm veins emptied, whereas the spiders remained full of blood. With the subject's arm held upright, a sphygmomanometer cuff was applied to the upper arm above the spider, and the pressure was raised to 170 mm. Hg. The spider was then stroked with the finger until it blanched. After the arm was lowered to a plane level with the heart, pressure was released within the cuff. The spider filled abruptly when the pressure was reduced to 85 mm. Hg. This study was confirmed by use of the reflecting mirrors previously described. When the pressure in the cuff was raised above 85 mm. Hg the pulsations ceased. They reappeared when the pressure was lowered to 85 mm. Hg or less. Systolic blood pressure at the brachial artery was 120 mm. Hg. It appears, therefore, that the pressure at which blood flows through the vessels of the spider is lower than the systolic pressure of the brachial artery and higher than the subject's venous pressure. Moreover, it is higher than the pressures ordinarily observed in the skin capillaries.[18]

Dilatation and Contraction. A fair definition of the structure of the spider was obtained by use of the dissecting microscope with a 40× magnification of Figure 1. Interfering glare of light from the skin was eliminated by applying a drop of oil to the under surface of a cover glass placed on top of the spider. Dilatation and contraction of the central vessel wall was visible in spiders of moderate size. The pulsation was augmented by exerting counterpressure on the cover glass. With this technique, pulsation was revealed even in the smaller vessels. However, in the small radiating branches, the pulsation was seen to be associated with a to-and-fro rush of blood through the long axis of the vessels. These branches were many times larger than capillaries at the finger nailbeds seen with the same magnification.

In the course of these studies with the dissecting microscope it became apparent that vascular changes in the skin of patients with liver disease were not confined to the spider. In 8 out of 15 patients with cirrhosis of the liver and vascular spiders, the skin of the arms revealed diffuse vascularity in other areas beyond the immediate vicinity of the spider. The vascularity was characterized by a network of widely dilated blood-vessels. In none of 15 control hospital patients were these changes observed. When erythema of normal skin was produced by rubbing with gauze, many fine capillaries with numerous punctate hemorrhages were seen, but no vessel

dilatation comparable to those described. Therefore, it is possible that the spider may indicate the presence of a widespread vascular change. This has been suggested by Fiessinger.[6]

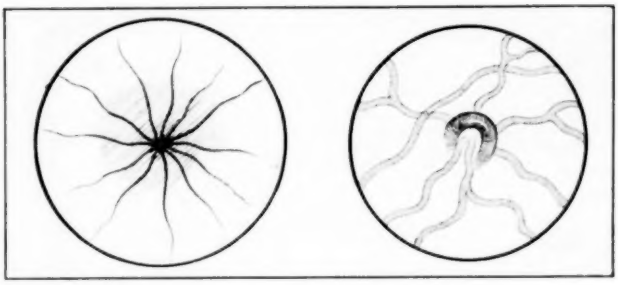
Pharmacologic Reactions. An attempt was made to observe the reactivity of the spider vessels to local stimuli. The intracutaneous injection of 0.1 cc. of 1:1000 solution of adrenalin hydrochloride at 1 cm. distance caused an area of blanching with a peripheral zone of hyperemia. As the pale area encroached upon the spider it caused marked narrowing of the finer vessels and moderate constriction of the larger central vessel. The intracutaneous injection of 0.05 cc. histamine phosphate (1:1000 solution) at a like distance was followed by a spreading pink flare. As this enveloped the spider, many tiny vessels (? capillaries) appeared. The larger vessels also seemed widened. However, due to limitations of technique it was not possible to measure these changes in a quantitative fashion.

Histologic Structure. Seven vascular spiders have been examined histologically; 2 specimens were obtained by biopsy and 5 at autopsy. In 4 instances the lesions were located on the dorsum of the forearm and in 3 instances on the anterior aspect of the thorax. Since these structures fade after death, it was necessary to outline areas for the purpose of identification before death.

The blocks of skin varied in their greatest dimension from 0.5 to 2.5 cm. The tissue was fixed in Zenker's solution for 18 hours, washed in tap water for 24 hours, dehydrated in alcohol, cleared in cedarwood oil, and embedded in paraffin. Serial sections, 6μ in thickness, were cut parallel to the skin surface. They were stained with Weigert's elastic tissue stain and hematoxylin, and they were counterstained with eosin.

On microscopic examination the vascular spider was seen to arise from an artery in the subcutis. This was observed in all instances. Histologically there are two distinct types. In one type the central vessel of the spider branches into smaller arteries which have the usual arterial structure. The smaller arteries branch successively into arterioles and capillaries. This was observed in 2 of 7 cases. The other type of vascular spider (seen in 5 cases) is quite different, and for the sake of convenience is described as the "glomus" type.

This latter type has a characteristic morphology. The afferent artery is of medium size, with a single layer of endothelium resting on an internal elastic lamella, and a media composed of circular muscle fibers. At the junction of this artery with the central vessel of the spider the endothelium and the internal elastic lamella become separated by a thick layer of cells with elongated, oval nuclei, abundant cytoplasm, and indistinct cell borders. The nuclei are about as long and half again as wide as those of the smooth muscle cells of the arterial media. They have a more diffuse distribution of chromatin and they are more widely separated. From



A *B*

FIG. 1.—*A*, Typical vascular spider as seen with naked eye. *B*, Typical vascular spider as seen with dissecting microscope (×40).

FIG. 2.—Section of part of the glomic connection between the afferent artery and the vascular "spider." The superior portion of the field is proximal to the afferent artery and shows the outer circular fibers of the media with elastica separating the newly acquired inner media. The inferior, more distal portion, has a much thicker inner layer of cells with elongated nuclei oriented in various directions. Here the stretched elastic lamella is still present but shows fragmentation in the lower part of the field. (Van Giesen elastic tissue and hematoxylin-eosin stain. ×230.)

FIG. 3.—A major branch of the vessel seen in Figure 2. Note the absence of both an outer circular layer and elastic fibrils The wall consists of cells like those of the inner media of the latter. (Van Giesen elastic tissue and hematoxylin and eosin. ×110.)

FIG. 4.—Small branches of the vessel seen in Figure 3. The walls consist of cells several layers thick, smaller and more closely spaced than those of Figure 3. These vessels branch into capillaries. (Van Giesen elastic tissue and hematoxylin-eosin stains. ×110.)

the varying shapes and directions of the long axes of the nuclei the cells seem to run circularly, longitudinally, and diagonally. The internal elastic lamella and the media of circular muscle of the afferent artery continue into the central vessel to form the outer portion of its wall. In the central vessel the elastic lamella becomes thinner, loses its wavy character and finally disappears after breaking into delicate threads (Fig. 2). The muscle fibers of the outer media retain the circular direction present in the afferent artery.

In its salient features, this junction of the afferent artery with the central vessel of the spider has the histologic traits of the "glomus," so thoroughly described by Popoff[23] and others.[5,13,16,20,27] However, it differs from the typical glomus by forming branches which ultimately connect with capillaries, instead of forming arteriovenous shunts or anastomoses. The central vessel follows a tortuous path through the corium, and near the dermis it branches into several smaller vessels. These branches retain the single layer of endothelium and the inner cellular layer, but they lack the outer coat of circular muscle. In these branches the media are 3 to 4 cells thick. The nuclei appear denser, smaller, and more darkly stained than those of the central vessel (*cf.* Fig. 3). These branches divide into smaller vessels of the same type and ultimately connect with capillaries, as seen in Figure 4.

Neither of the types of "vascular spider" resembles a tumor. The simpler type, consisting of dilated arteries, probably results from hyperplasia or hypertrophy of preëxisting arteries. It is unlikely that a physiologic or functional change alone could make arteries of this size visible through the skin. The more complex type with vessels resembling the afferent arteries of the glomus, suggests a metaplastic change of an artery to resemble glomus vessels and hyperplasia of the newly formed vessels. There are several reasons for this interpretation. *First*, these latter structures were found in regions where the glomus (arteriovenous anastomoses) has not been described. *Second*, the glomus vessels of the spider branch into capillaries and do not connect directly with veins. This implies that they are not derived from preëxisting arteriovenous anastomoses. *Third*, these vascular spiders tend to increase in size and number during exacerbations of the signs of cirrhosis, whereas they regress or even disappear during remissions of the disease.

Discussion. Congenital telangiectases have been described as dilated vascular channels lined by a single layer of endothelium, but lacking coats of elastic tissue and smooth muscle.[6,9,14] Osler and Bogaert believed them to be venous dilatations. Memmesheimer[21] pointed out associated degenerative changes in the supporting tissues. His cases, however, resembled diffuse venous ectasia rather than vascular spiders.

In several descriptions of telangiectases associated with liver disease an arterial structure has been implied. Gilbert and Herscher[8]

described a conglomeration of vessels of varying size, with irregular lumen, with swollen endothelium, and with a vessel wall usually thickened and studded with many nuclei. Loeper[19] and his associates interpreted the vessels as new formed arterioles. Weber[28] described one case of "pulsating stellate nævus" consisting of a superficial layer of dilated capillaries and beneath these, in the deeper cutis, a spiral or plexiform artery.

In the present studies certain of these differences possibly may be reconciled if the level of the histologic sections, as related to the skin surface, is taken into consideration. The superficial branches of the vessels, indeed, are vascular channels, whose walls are composed of a single layer of endothelium. On following the course of these branches in serial sections, they are seen to emanate from a larger vessel; tortuous, thick-walled, and finally conforming in its structure to an artery.

The preceding observations reveal that the vascular spider originates from the arterial side of the vascular tree and that it is of the order of a small artery. This is demonstrated by studies on the direction of blood flow, pulsations, contractility, intravascular pressure, and histologic structure of the vascular spider. The response to the injection of adrenalin and of histamine likewise is consistent with the behavior of an artery or of an arteriovenous anastomosis.[11,12]

The problem has been complicated by the interchangeable use of the terms "spider telangiectasis" and "spider angioma" for these structures. The term telangiectasis is restricted usually to small lesions, as described in this report, whereas angioma refers to the larger, elevated lesions. Since both actually do pulsate, and since both are seen frequently in the same patient, it is likely that the differences are more in degree than kind.

It is assumed in the literature that the congenital and the acquired lesions are similar. The acquired type of spider, described in this paper, does not conform to descriptions of the congenital lesions, previously mentioned. Also it is clear from the present studies that the vascular spider should not be confused with *congenital hemangioma*.

There have been several reports suggesting a causal relationship between the vascular spider seen in liver disease and the congenital spider.[7,28–30] These are based on case reports in which vascular lesions appeared in advance of clinical signs of liver disease. The inference has been drawn that this process may share a background in common with liver disease. It should be pointed out that cirrhosis of the liver may long antedate any clinical evidence of the disease. Indeed, it may remain clinically latent throughout life. Consequently, in those cases lacking a family history of vascular spiders, latent disease of the liver may exist.

Conclusions. 1. The vascular spider, associated with disease of the liver, has the physiologic characteristics of an artery. This has

been demonstrated by studies on direction of blood flow, pulsations, contractility, intravascular pressure, and pharmacologic reactions.

2. In serial sections, the histologic characteristics of 2 lesions are those of an artery and its arteriolar branches. In 5 others they resemble, in a magnified form, the arterial segment of an arteriovenous anastomosis (glomus). However, the branches of these vessels are continued into capillaries, and are not directed into veins.

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TEMPERATURE AND BRAIN METABOLISM*

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Changes of body temperature have been widely used as therapeutic agents. Increased temperature has been successfully employed in the treatment of general paresis and in gonorrheal infec-

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tion. The present report is concerned with the effects of temperature changes on cerebral metabolism.

Method. Metabolism of the brain *in vivo* was estimated from chemical analyses of the arterial and venous blood entering and leaving the brain. Samples of blood coming from the brain were taken from the internal jugular vein by the method of Myerson, Halloran and Hirsch[5] and the arterial blood samples were collected without contamination with air and analyzed for oxygen and carbon dioxide content,[7] glucose,[3] and lactic acid.[2] The oxygen capacity of the arterial blood was determined in each case. The velocity of blood flow in the peripheral circulation was estimated by the cyanide circulation time method of Robb and Weiss.[6]

The effect of fever therapy on the cerebral metabolism was studied on 15 patients suffering with general paresis. Observations were made before the rise of temperature and at various intervals during the period temperature was elevated. In 7 instances fever was induced by the injection of 0.4 cc. of triple typhoid vaccine intravenously. In 7 others temperature was raised with inductotherm and 1 patient was studied during malarial fever. These studies were not limited to patients. The metabolism of excised cerebral tissues was estimated at various temperatures from 25° C. to 45° C. Cerebral cortex of rats were minced and the oxygen uptake was determined in the Warburg apparatus.

Results. It should be emphasized that with all three methods of producing fever, the effects in general were the same, that is, the metabolic A:V oxygen differences increased. In a typical example, Patient 11 (Table 1), the oxygen difference at a temperature of 98° F. is 5.15 vol.% and at 104.4° F. rises to 7.61 vol. %. Finally, at 106° F., a value of 9.14 vol. % is attained. In 11 of 15 patients the oxygen difference increased at least 2 vol. % during fever. The results of the oxygen capacity of the blood revealed no significant changes in 8 instances but 3 increases and 5 decreases were also observed. The oxygen capacity varies with the number of red blood cells and is therefore an indicator of the concentration of the blood. Because of the profuse perspiration during the fever, an increased concentration of the blood might be expected but the liberal ingestion of fluids probably overcame such a change.

The A:V difference of glucose disclosed an absorption of glucose by the brain in 45 of 49 experiments. In only one case did the brain pour a significant amount of glucose into the blood. No relationship between the volume of oxygen and the amount of glucose absorbed by the brain was observed. The concentration of lactic acid frequently was moderately increased by fever but in most cases the lactic acid content of blood was not changed significantly as a result of passage through the brain.

The observations on the effect of temperature on the metabolism of excised brain tissue are presented in Table 2 and Chart I. It may be seen in Chart I that the metabolic rate of the brain increases from 25° C. to 44° C. during a period of observation of 20 minutes. The rate of increase from 25° C. to 30° C. is 7.3%; from 30° C. to 35° C., 9.2%; from 35° C. to 40° C., 8.4%; and from 40° C. to

TABLE 1.—OBSERVATIONS MADE DURING THREE TYPES OF FEVER THERAPY.

Patient No.	Temp., °C	Oxygen, A-V diff.	Circulation time.	Blood pressure.	Pulse.	Arterial. Lactic acid.	Arterial. Sugar.
			Inductotherm Therapy.				
1	99·4	5·16	17·0	150/72	100	17	81
	101·8	5·05	10·0	156/106	90	20	90
	103·8	7·24	7·0	104/96	120	31	141
2	100·8	6·91	15·4	156/110	100	16	97
	103·8	10·99	11·8	147/75	160	25	101
3	98·6	9·37	14·0	122/90	88	13	110
	102·6	7·46	9·2	176/130	130	31	127
	104·0	11·38	7·2	160/100	130	24	124
4	98·6	6·36	16·0	90/50	90	12	83
	101·8	5·85	15·0	104/58	90	13	77
	102·6	6·66	12·2	104/50	120	24	88
	105·0	10·62	10·0	112/38	122	21	88
5	99·4	5·30	18·0	92/60	90	22	81
	101·4	3·68	12·2	100/60	70	12	94
	103·0	2·61	9·2	112/60	86	17	101
	104·8	5·39	10·4	106/50	96	21	105
6	99·0	4·62	11·0	117/68	90	16	77
	101·0	6·60	13·0	122/80	100	16	79
	103·6	7·29	9·0	136/60	120	16	88
	105·4	7·86	7·4	134/70	120	19	98
7	98·6	6·62	13·2	134/90	88	26	97
	103·4	7·70	11·0	134/90	140	22	97
	105·6	8·05	9·6	118/80	140	26	110
	106·0	6·31	7·2	134/90	120	24	110
			Typhoid Therapy.				
8	98·6	7·75	20·0	126/94	80	15	95
	105·0	15·82	17·0	138/86	120	36	119
9	98·8	6·93	15·0	126/90	80	26	92
	105·0	7·88	11·0	108/50	100	46	112
	105·3	7·09	4·0	100/50	130	31	129
10	98·8	4·91	13·0	104/70	88	17	79
	101·6	6·98	10·6	94/42	110	16	95
	104·0	7·17	9·0	100/60	130	28	90
11	98·0	5·15	17·6	158/106	78	20	97
	100·4	6·55	11·0	156/96	108	20	92
	102·0	6·63	10·0	155/70	96	27	84
	104·4	7·61	13·0	140/62	130	17	102
	106·0	9·14	7·4	125/70	140	27	129
12	98·6	10·26	22·0	122/80	80	22	99
	101·2	10·83	13·0	120/70	100	20	100
	105·6	9·32	14·0	120/60	120	27	119
13	98·6	4·45	12·4	120/70	80	11	72
	100·8	8·21	15·6	90/30	120	20	74
	103·0	8·76	21·8	96/35	132	26	77
14	98·8	5·15	14·4	117/80	90	15	131
	102·8	8·66	14·8	90/80	100	19	93
	105·4	10·17	13·6	84/62	130	21	92
	103·8	10·60	18·8	98/68	100	25	110
			Malarial Therapy.				
15	99·0	3·56	17·0	116/70	84	..	122
	102·0	6·18	14·2	104/70	100	..	159
	104·2	9·34	12·6	110/50	100	..	141

44° C., 6.2%. However, above 44° C. or 111° F., this increase is not maintained. This is seen more clearly in the lower curve which presents the observations made during the 50th and 60th minutes and reveals a rapid fall of the oxygen uptake with temperatures above 40° C.

TABLE 2.—TEMPERATURE AND CEREBRAL METABOLISM.

Oxygen uptake is calculated per 100 mg. of minced rat brain per hour.

	0 to 20 minutes.		50 to 60 minutes.	
Temperature.	Number of observations.	Average oxygen uptake.	Number of observations.	Average oxygen uptake.
25° C.	14	69	11	51
30° C.	11	100	10	85
33° C.	9	131	9	105
37° C.	37	189	34	182
38° C.	19	216	19	183
40° C.	24	245	19	176
42° C.	45	263	21	139
44° C.	27	315	23	80
45° C.	19	310	18	44

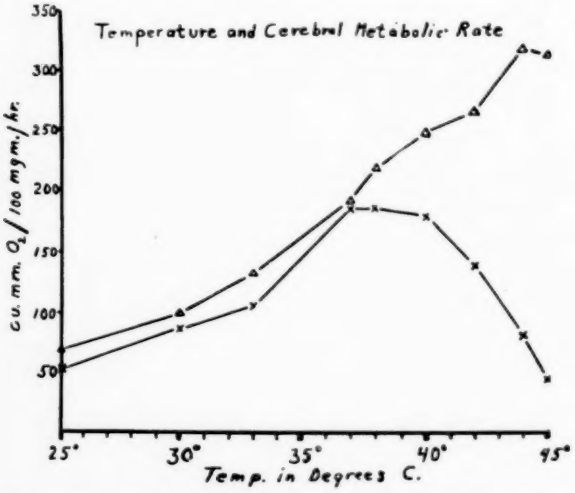

CHART I.—Upper curve indicates metabolic rate for first 20 minutes at various temperatures. Lower curve indicates metabolic rate from 50th to 60th minutes.

Discussion. The present results reveal that the brain takes part in the increased oxygen uptake of the body which is characteristic of fever. DuBois[1] has observed an average rise of 13% in the metabolic rate of the body for each degree Centigrade. An apparent augmentation of cerebral metabolism is indicated by an increase of the A:V difference greater than expected from DuBois' observations. For example, in Experiment 11, a rise of 8° F. should elevate metabolism approximately 55%, yet the change of the A:V difference from

5.15 vol. % to 9.14 vol. % represents an acceleration of 77%. Such an increase may be explained in one of two ways: 1, the brain responds with a rise in metabolism greater than other parts of the body during fever; or 2, the circulation rate through the brain is slower during fever thus making for a larger A:V difference.

Other evidence indicates that the blood flow through the brain may be diminished during fever, or at least not increased to the same extent as the cerebral oxygen uptake. It is well known that elevation of body temperature is combated principally by greater loss of heat from the body. Heat losses are mediated by an increased blood flow through the periphery. This redistribution of the circulating volume deprives the other parts of the body, including the brain, of the quota of blood. An increased blood flow through the periphery is indicated by: 1, the shorter circulation time observed with the cyanide method of Robb and Weiss; and, 2, a vasodilation evidenced by the warm flushed skin of the patients. It, therefore, seems probable that cerebral circulation is often diminished by fever and that the increase of metabolism is not as great as indicated by the A:V differences.

In order to obtain further information on this point and exclude the factor of blood flow, the metabolism of excised cerebral tissues was studied at various temperatures from 25° C. to 45° C. An acceleration of metabolism was noted in all temperatures from 25° C. to 44° C. for the first 20 minutes. Up to a temperature of 44° C. metabolism is accelerated for the first 20 minutes as seen in the upper curve, but the lower curve which shows the effect on metabolism from the 50th to the 60th minutes reveals a depression at temperatures above 40° C. It is apparent that some changes detrimental to cerebral oxidation occur at high temperatures. These alterations may be the cause for the occasional death which is observed with hyperpyrexia.[4]

Three chief principles are active in normal metabolism: oxygen, enzymes, and food. During fever the interactions of these three principles are accelerated. Oxygen is utilized more rapidly and the temperature of the body is raised, but this process cannot be accelerated indefinitely. With regard to temperature, enzymes are formed of two parts, first, thermostabile, and, second, thermolabile, protein in nature. With increasing temperature a point will be reached at which the protein parts of the enzyme systems are changed. Until this critical temperature of the protein parts of the enzyme is reached, the delivery of energy for cerebral metabolism is accelerated, but after the proteins are changed, the enzyme can no longer take part in the delivery of cerebral energy. Thus, as the cell proteins are changed by the heat, the cells must simultaneously die for want of the energy necessary to keep them alive. This is well illustrated by the results obtained on excised minced cerebral tissues. As the temperatures rise above 37° C. the rate of acceleration is not main-

tained even for the first 20 minutes. During the 50th to the 60th minutes this decrease is more pronounced and especially so with temperature from 40° C. to 44° C. Dixon studied rates of respiration in sliced cortex of the rabbit's brain and stated that respiration was only slightly higher at 42° C. than at 37° C. At 45° C., however, respiration was increased 100% above that at 37° C. In the present observations the increment between 37° C. and 42° C. was 39% and the one between 37° C. and 44° C. was 66% for the first 20 minutes. The increase of respiration from 30° C. to 37° C. is 90%. Thus the increase from 30° C. to 37° C., is in good agreement with DuBois' observations while the rise from 37° C. to 44° C. is smaller. This smaller increment with the higher temperature may be attributed to the greater susceptibility of excised cerebral tissue to increase of temperature. Such a factor may be emphasized because rat brain possesses a high rate of metabolism and may therefore suffer more from a rise of temperature. On the other hand, DuBois' observations may not apply directly to the brain for they were made on the entire respiratory exchanges of patients and not on the brain alone.

Finally a word may be said in regard to the effect of fever on the course of general paresis. As suggested above, increase of temperature may damage brain and the therapeutic effect may be ascribed in part to the greater susceptibility of the diseased portions which may thus be destroyed. Another factor may be more important and this depends upon the development of a non-specific defense against the spirocheta pallida. This is general tissue response as evidenced by the increased protein content and greater cell count of cerebral spinal fluid of the luetic patient. It is well known that patients with such a reaction have a better prognosis and moreover derive benefit from fever therapy. These defensive responses are probably based on enzymatic activities. The latter are accelerated by fever and account at least in part, for the benefit derived from this form of therapy.

Conclusions. Fifteen patients with general paresis were subjected to one of three forms of fever therapy and the arterial A:V differences of the cerebral blood were determined. In 11 of 15 instances the A:V difference increased by more than 2 vol. %. In most cases the augmentation of the A:V difference was greater than could be explained by the rise of temperature. Such a large increase may be due to changes in blood flow not commensurate with those of the oxygen uptake of the brain. In minced cerebral tissues from rats the increase of respiration from 30° C. to 37° C. is 90%, in accordance with expectation of chemical reactions. In contrast the rise from 37° C. to 44° C. is only 66%. This damaging effect of high temperature is increased with duration.

Though the results of changes of temperature are many, they are mediated chiefly by the effects of enzyme systems which make energy available for the body. With rise of temperature these

systems yield a more rapid flow of energy thus accelerating all actions. However, an increase of temperature which is critical may cause an irreversible change of the thermolabile portion of these enzymes, thus interfering with delivery of energy and in extreme cases causing death.

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PATHOLOGIC CHANGES FOLLOWING PROLONGED ADMINISRATION OF SULFATHIAZOLE AND SULFAPYRIDINE.

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Following the synthesis of 2(p-amino-benzene-sulfonamido) thiazole by Fosbinder and Walter[7] and Lott and Bergeim,[15] studies have been made of its pharmacology, toxicology and therapeutic activity.[2,4,9,10,12,16,18,24,25] The lesions produced in laboratory animals by prolonged administration of sulfathiazole and sulfapyridine have also been studied.

Shortly after the introduction of sulfapyridine reports began to appear concerning certain toxic manifestations. These were concerned for the most part with effects on the hematopoietic system and on the urinary tract. Lloyd, Erskine and Johnson[14] noted some depression of the neutrophils following administration of sulfapyridine to patients with gonorrhea, and later Coxon and Forbes[5] reported the first case of agranulocytosis. Many clinical reports followed. Wien[26] noted no change in the blood picture of rats given as much as 4 gm. per kilo daily for 2 weeks in the form of an aqueous suspension given orally. Toomey[23] found that a definite anemia developed in monkeys given sulfapyridine; no details are given.

Southworth and Cooke[21] were the first to report effects on the urinary tract in man. These, which included, in 3 cases, hematuria, albuminuria, crystals of the drug in the urine, renal colic, anuria lasting for 14 hours, and nitrogen retention, ceased when administration of sulfapyridine was stopped. Snapper, Liu, Chung, Yü

and Sun reported 4 cases of hematuria, 2 with renal colic, following treatment with sulfapyridine.[20] One case died and at autopsy a stone consisting of 55.3% acetyl-sulfapyridine and 1.9% sulfapyridine was found. Stokinger[22] found that crystals of acetyl-sulfapyridine appeared in the urine of the rabbit and man following ingestion. Antopol and Robinson[1] administered sulfapyridine to monkeys, rabbits and rats. Single large doses or repeated smaller doses gave rise to uroliths of acetyl-sulfapyridine. Thus 0.25 gm. per kilo in monkeys, 10–15 gm. per kilo in rabbits, and 5 gm. per kilo in rats given daily for 10 days produced uroliths. With single large doses crystals appeared in the urine in a few hours. Within 24 hours calculi appeared in the bladder; ureters and renal pelves showed dilatation, or masses of crystals filled the pelvis and extended into the medulla of the kidney. The organs were large and edematous and occasionally showed pyelonephritis. Gross, Cooper and Lewis[8] studying rats killed by treatment with sulfapyridine found dilatation of ureters and renal pelves and large soft kidneys. Concretions were frequently present producing more or less complete urinary obstruction and contained 6.4% sulfapyridine and 64.1% acetyl-sulfapyridine. Toomey,[23] autopsying monkeys given sulfapyridine found blood and crystals in the urine, concretions in bladder, ureters and renal pelves, dilatation of the pelves, swollen kidneys and pyelonephritis. Molitor and Robinson[17] gave sodium sulfapyridine orally to mice, rats, rabbits and monkeys as a 10% aqueous solution (pH 11.4). Single doses of 3–4.5 gm. per kilo produced gastric irritation in mice, rats and rabbits, and uroliths in rats and rabbits. When given daily for 10 days, 0.25 gm. per kilo produced gastric irritation and uroliths in monkeys and 2 gm. per kilo had the same effect in rats. Oral or intravenous administration of acetylated sodium sulfapyridine produced uroliths in mice, whereas uroliths were not found after the administration of the non-conjugated drug.

Wien[26] found that daily oral administration of 4 gm. per kilo of an aqueous suspension of sulfapyridine to rats for 2 weeks produced a retardation of the growth curve. One gram per kilo had no such effect.

Wien[26] also noted that the spleen in his rats was normal, and Johannsen and St. George[11] found no gross or histological lesions in the lungs, heart, liver, kidneys or spleen of mice receiving lethal or sublethal doses of sulfapyridine.

A brief account of pathologic studies in monkeys, rats and mice following prolonged administration of sulfathiazole and sulfapyridine has been given elsewhere.[19] Cooper, Gross and Lewis[4] have noted that sulfathiazole and sulfamethylthiazole, like sulfapyridine, produce renal concretions in rats.

Technique. *Mice.* Sulfathiazole and sulfapyridine were administered to Swiss mice, weighing between 11 and 20 gm., either at 1% or 2% in the standard Sherman dry diet.[3,13] There were 22 animals on each 1% diet

and 30 on each 2% diet. The feeding of the drug was continued for 4 weeks. It was found that, as others had shown,[3,13] the mice ate the drug diet mixture almost continuously. Consumption reached a peak around midnight and fell to a low level at 6 o'clock in the morning. After the first 2 days, during which the mice ate relatively poorly, the consumption of food was equivalent to that of the Sherman diet without drug. The only exception to this was in the case of the 2% sulfathiazole diet. Here the consumption of drug was more irregular and half of the mice ate less on this diet than on any other. In all cases, save one, it is to be noted that the latter were those that succumbed early to the toxic effect of the 2% sulfathiazole diet and part, if not all, of their small food consumption must be ascribed to anorexia. Mice receiving the diet containing 1% sulfathiazole consumed on an average 2.38 gm. of drug daily per kilo of starting weight (variation 1.77 gm. to 3.09 gm.). On 2% sulfathiazole diet the average amount consumed daily was 2.6 gm. of drug daily per kilo of starting weight (variation 1.03 gm. to 4.9 gm.). For 1% sulfapyridine diet the average was 2.26 gm. of drug daily (variation 1.65 gm. to 2.96 gm.). On the 2% sulfapyridine diet the figures were 3.37 gm. per day average (variation 2.8 gm. to 4.17 gm.).

Rats. In groups of 18, rats were administered the two drugs incorporated with the standard S–50 dry diet as 0.5% or 1%. S–50 diet consists of: Whole wheat, 29%; yellow corn, 30%; milk powder, 21%; linseed meal,7%; cod-liver oil, 1%; meat scrap, 10%; alfalfa, 2%.

Food consumption, and hence amount of drug eaten, was not measured continuously but was determined twice at an interval of 1 month. After the rats had been on the diets for about 2 weeks and were then approximately 37 days old, the average amounts of drug eaten per kilo body weight per 24 hours were 0.47–0.48 gm. for 0.5% sulfathiazole, 0.62–0.75 gm. for 1% sulfathiazole, 0.41–0.43 gm. for 0.5% sulfapyridine, and 0.68–0.72 gm. for 1% sulfapyridine. One month later after the rats had grown considerably, the consumptions of drug, in terms of amounts eaten per kilo of body weight per 24 hours, were 0.26 gm. for 0.5% sulfathiazole, 0.55–0.64 gm. for 1% sulfathiazole, 0.26–0.31 gm. for 0.5% sulfapyridine, and 0.53 gm. for 1% sulfapyridine.

Monkeys. Two experiments were run with monkeys. In the first case the animals were given daily for 14 days 0.4 gm. of sulfapyridine or sulfathiazole per kilo of initial body weight. The drugs, as a 10% suspension in 5% gum acacia, were given once a day by means of a stomach tube. In this series there were 3 monkeys given sulfathiazole (weights from 3.4 to 4.7 kilos) and 3 given sulfapyridine (weights from 2.5 to 4.3 kilos). In the second series the only difference was that medication was continued for 21 days. In this case there were 4 animals receiving sulfathiazole (weights from 2.4 to 4.3 kilos) and 4 receiving sulfapyridine (weights from 3.0 to 4.7 kilos).

Results. *Mice.* Mice receiving either dose of sulfapyridine or the lower dose of sulfathiazole remained well throughout the 4-week period. Of those receiving the diet containing 2% sulfathiazole, 77% died. Deaths began on the 3rd day, 13% were dead by the end of the 5th day, and 70% by the end of the 20th day. The mice which survived on the 2% sulfathiazole diet often were those which consumed the food most heartily. Thus the average amount of diet consumed daily by these survivors was 3.29 gm. per kilo of initial body weight and the amounts varied from 2.34 to 4.9 gm.

All mice which survived were killed at the end of 4 weeks and autopsied. Those dying during the test period (2% sulfathiazole)

were also autopsied. No mice receiving either dose of sulfapyridine showed any gross pathologic changes. In those mice receiving 1% sulfathiazole the only gross pathologic change noted was that 13% showed a very small dark spleen and in 61% this change was also present though to a lesser degree. In the survivors on the 2% sulfathiazole diet the only changes noted in the gross were very small spleens in 2 instances and large pale kidneys in 2 instances. In those animals on the 2% sulfathiazole diet which died, no changes were noted until the 4th day. On that day and subsequently gross changes were seen in spleen and genito-urinary tract. The spleen was dark and either small or very small in 65%. The kidneys were large and pale in 45% and there was often definite hydronephrosis (Fig. 1). Concretions were found in the pelvis of the kidney or in the bladder in association with hematuria in 25%. These concretions when analyzed yielded about 25% free and 75% conjugated sulfathiazole.

Microscopically, those mice receiving 1% sulfapyridine diet showed no abnormalities in lungs or spleen. The livers of all mice in this group showed cloudy swelling which was very marked in half the animals (Fig. 2). The change in the early stages was in the center of the lobules. In 1 case there was some fatty infiltration. A few mice on this diet showed slight dilatation of the convoluted tubules of the kidney. These dilated tubules occasionally contained débris or even cellular casts.

On the 2% sulfapyridine diet lungs, spleen and central nervous system were normal microscopically. In the liver the same changes were seen as appeared in mice on 1% sulfapyridine, except that in 1 case a few foci of necrotic cells were found (Fig. 3). In the kidney changes were similar to those found on the 1% diet.

In those mice receiving 1% sulfathiazole the lungs were normal. In the spleen microscopic changes were found in 41%. These were present only in the Malpighian corpuscles. In a few cases germinal centers were hyperplastic. In others they were smaller than normal, appeared disorganized, or had even disappeared and pyknotic cells were present. In some cases, moreover, the small lymphocytes of the mantle zone had disappeared or decreased in number. In the kidney the changes seen were similar to those seen in mice receiving 1% or 2% sulfapyridine diets. They were perhaps slightly more extensive and in 1 case many of the convoluted tubules were lined with hyaline necrotic cells. Changes in the liver were similar to those seen with sulfapyridine.

In the survivors on the 2% sulfathiazole diet the lungs and central nervous system were normal. Lesions in the spleen, found in 50%, consisted in disorganization of the germinal centers with pyknosis of many of the lymphoblastic cells and their ultimate disappearance. (Figs. 4 and 5.) In the liver there was cloudy swelling as with sulfapyridine (Fig. 6). In 2 cases fatty infiltration was noted

PLATE I

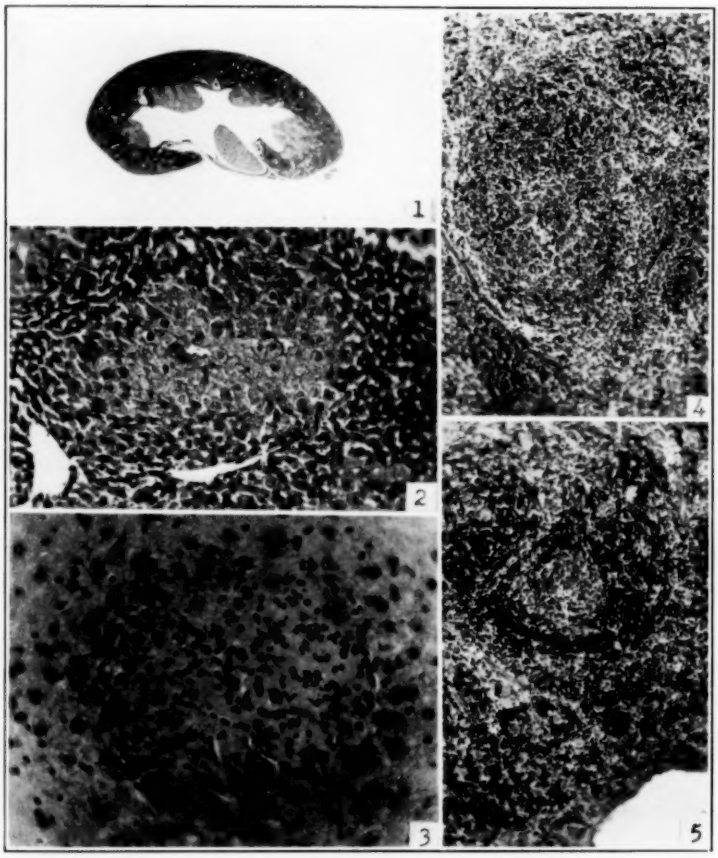

FIG. 1.—Sulfathiazole. Mouse kidney showing hydronephrosis. (× 7. H. and E.)
FIG. 2.—Sulfapyridine. Mouse liver showing cloudy swelling. (× 110. H. and E.)
FIG. 3.—Sulfapyridine. Mouse liver showing necrosis and leukocytic infiltration. (× 260. H. and E.)
FIG. 4.—Normal mouse spleen showing Malpighian corpuscle. (× 110. H. and E.)
FIG. 5.—Sulfathiazole. Mouse spleen showing alterations in the germinal center of a Malpighian corpuscle and loss of lymphocytes from the marginal and mantle zones. (× 110. H. and E.)

PLATE 2

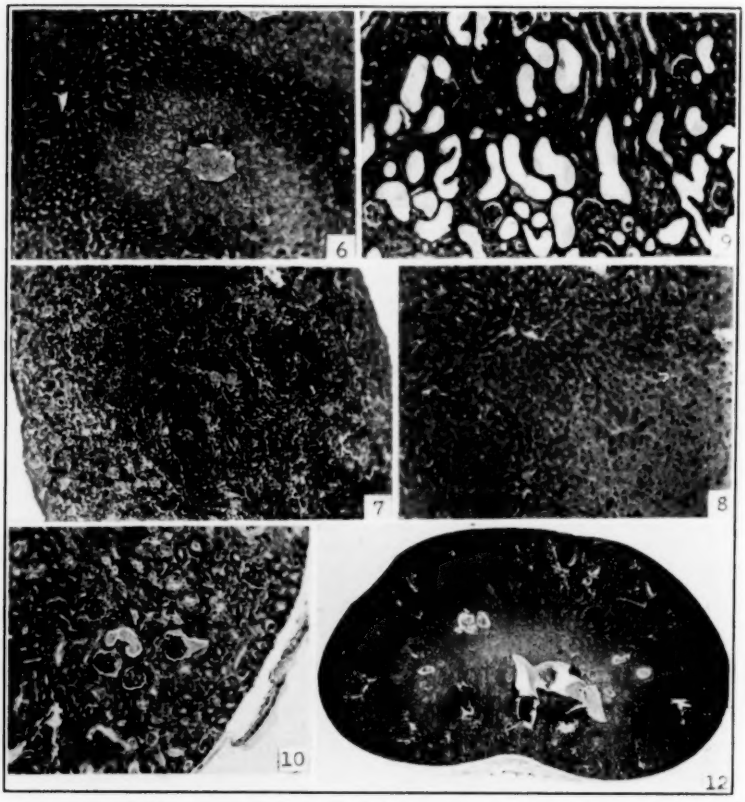

FIG. 6.—Sulfathiazole. Mouse liver showing cloudy swelling. (× 110. H. and E.)

FIG. 7.—Sulfathiazole. Mouse spleen showing disappearance of all lymphoid elements from the Malpighian corpuscles. The entire width of the spleen appears in the illustration demonstrating the decrease in size of the organ. (× 110. H. and E.)

FIG. 8.—Sulfathiazole. Mouse liver showing area of necrosis. (× 110. H. and E.)

FIG. 9.—Sulfathiazole. Mouse kidney showing dilatation of tubules in the cortex. (× 110. H. and E.)

FIG. 10.—Sulfathiazole. Mouse kidney showing dilatation of glomerular capsules and tubules with albuminous casts. (× 110. H. and E.)

FIG. 12.—Sulfathiazole. Rat kidney showing maximum change produced. Slight dilatation of the renal pelvis. (× 7. H. and E.)

PLATE 3

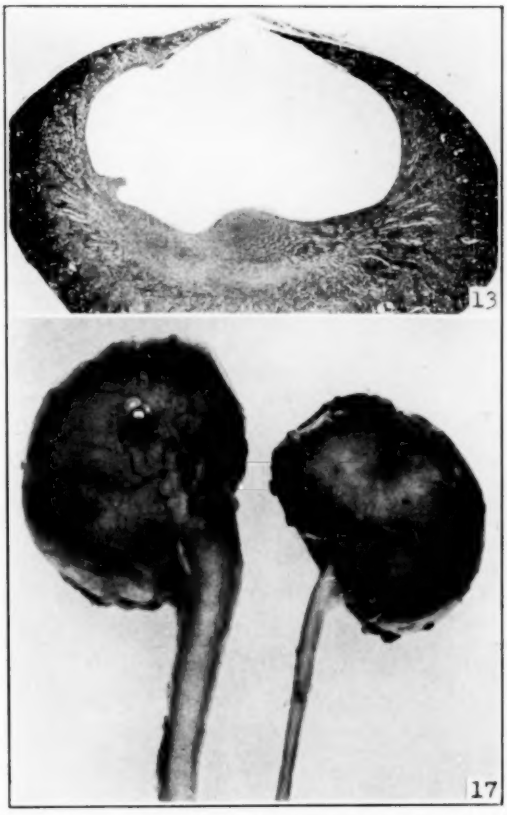

FIG. 13.—Sulfapyridine. Rat kidney showing hydronephrosis with compression of the organ and dilatation of tubules in cortex and medulla. (× 7. H. and E.)
FIG. 17.—Sulfapyridine. Monkey 49. Kidney. Hydronephrosis and hydroureter on the right side.

PLATE 4

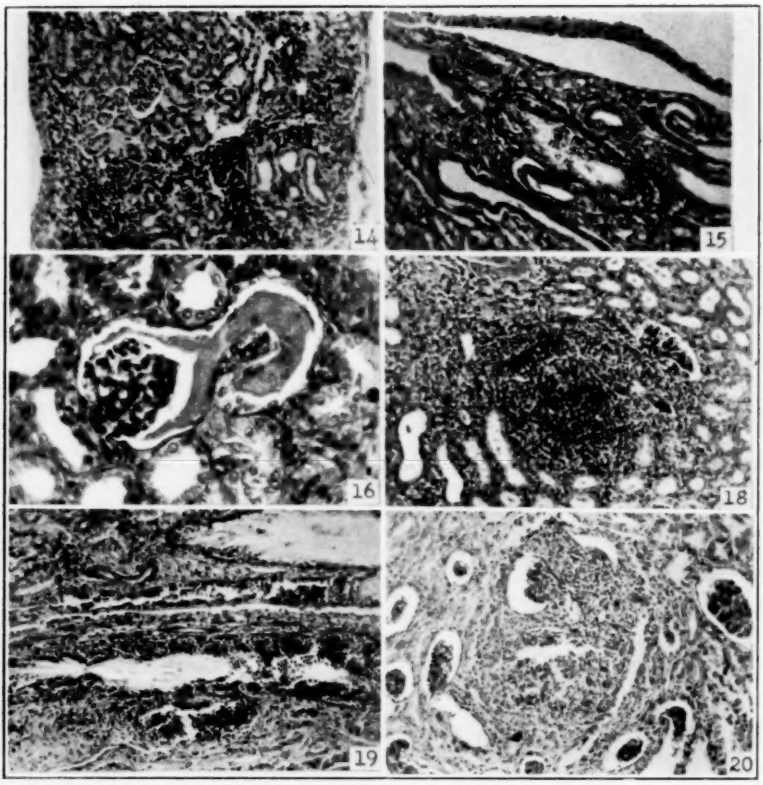

FIG. 14.—Sulfapyridine. Rat kidney showing the total width of the organ. Some tubules dilated, others collapsed and surrounded with scar tissue. (× 110. H. and E.)

FIG. 15.—Sulfapyridine. Rat kidney showing the outline of crystals in a tubule and surrounding leukocytic infiltration. (× 110. H. and E.)

FIG. 16.—Sulfapyridine. Monkey kidney showing albuminous cast filling the glomerular capsule and commencement of the tubule. (× 260. H. and E.)

FIG. 18.—Sulfapyridine. Monkey kidney showing leukocytic infiltration in and around tubules forming an abscess. (× 110. H. and E.)

FIG. 19.—Sulfathiazole. Monkey kidney showing the outline of crystals in tubules and surrounding leukocytic infiltration. (× 110. H. and E.)

FIG. 20.—Sulfathiazole. Monkey kidney showing leukocytes in and around the tubules. (× 110. H. and E.)

at the periphery of the lobule and in 2 others, small areas of hyaline necrosis with cellular infiltration were seen. In half of the cases very little was to be seen in the kidney except dilatation of the convoluted tubules which contained débris or a few casts. In the other half the changes were more extensive. Both the convoluted, and in 2 cases also the collecting, tubules were greatly dilated and contained hyaline and cellular casts. In 1 case there were marked changes in the cells lining the convoluted tubules which amounted in places to complete necrosis. In the same kidney blood was present both in Bowman's capsule and in the convoluted tubules. In another case it was possible to see in the collecting tubules angular outlines obviously indicating where crystals of drug had been. Such tubules were surrounded with leukocytes.

In those mice which succumbed to the 2% sulfathiazole diet similar microscopic changes were observed. In 1 case there was a terminal pneumonia but lungs from the others were normal. No lesions were observed in the brain or spinal cord. The changes in the spleen were more marked. In most instances not only had the germinal centers of the Malpighian corpuscles disappeared completely but, in addition, the mantle and marginal zones of lymphocytes had disappeared, leaving nothing but foci of collapsed splenic stroma (Fig. 7). The changes in the liver of those that died were similar in type to those seen in the mice killed after 28 days but were less in degree. In 1 case, however, there were two large areas of necrosis (Fig. 8).

All mice dying after the 3rd day showed lesions of the kidney. These changes were the same as those seen in the mice killed after 28 days. Dilatation was not confined to the convoluted tubules (Fig. 9) but in 2 cases involved the glomerular spaces (Fig. 10). Cytoplasmic changes in the cells of the cortical tubules were also more frequent. Blood was seen in Bowman's capsule and the convoluted tubules in 1 case and the outlines of crystals in the collecting and convoluted tubules in another.

Rats. All rats survived for the 57-day period of the test. The gain of weight, however, was significantly less in the rats receiving sulfapyridine. Rats receiving ½% sulfathiazole in the diet gained weight equally with the controls (Chart 11). At the end of the 57 days complete blood counts were made on all rats, which were then killed. All blood counts were normal. At autopsy in those animals receiving ½% sulfathiazole, 2 out of 15 showed fine yellow streaks in the medulla of the kidneys. The remainder were normal. Of 18 animals receiving 1% sulfathiazole 5 showed similar changes in the kidneys. Only 3 of 17 rats receiving ½% sulfapyridine were normal in the gross. One of the others showed only what appeared to be deposits of crystals in the medulla of the kidneys. The others showed concretions in bladder, ureters or pelvis, or all three, with hydroureter and hydronephrosis in 10 cases, and marked hem-

aturia in 1. Of rats on 1% sulfapyridine 5 out of 16 were normal. The others showed concretions in bladder, ureters or pelvis, or all three sites, with hydroureter and hydronephrosis in most cases.

Microscopically, in the rats on ½% sulfathiazole the liver, spleen and bone-marrow were normal. The kidney was also normal except in two of those examined. In one of these there was dilatation of all renal tubules and in the other, slight dilatation of the renal pelvis (Fig. 12) and more marked dilatation of all tubules. These tubules contained a few casts and some débris; in a few places cytoplasmic changes were seen in the lining cells. On the 1% sulfathiazole diet liver, spleen and bone-marrow again were normal. The kidney changes resembled those seen in the group on ½% sulfathiazole.

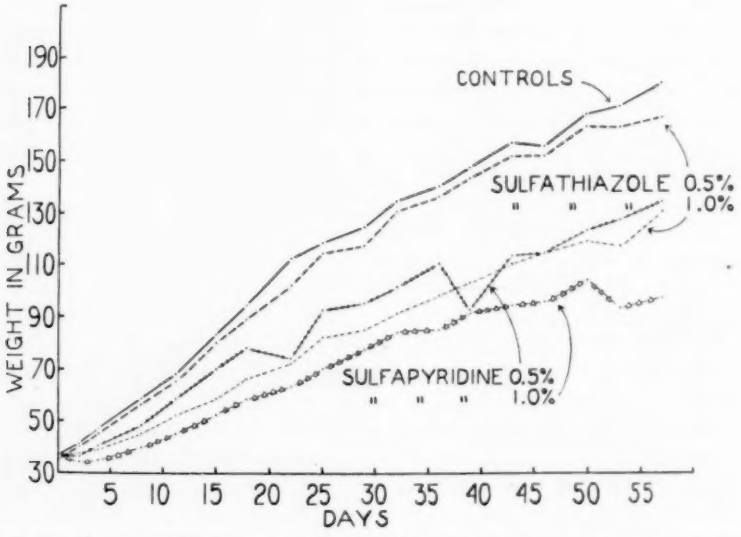

CHART 11.—Growth curves of groups of rats receiving control diet and diets containing sulfapyridine or sulfathiazole. (Reproduced from Van Dyke, H. B., Greep, R. O., Rake, G., and McKee, C. M., Proc. Soc Exp. Biol. and Med., **42**, 410, 1939.)

The liver, spleen and bone-marrow were normal in animals receiving either ½% or 1% sulfapyridine in their diet. The changes in the kidneys were similar in the two groups. There was marked dilatation of the pelvis of the kidneys (Fig. 13) in all but 1 case and in most instances this hydronephrosis had produced in turn collapse and destruction of most of the tubules and glomeruli and their replacement by scar tissue (Fig. 14). Those tubules which were not collapsed were dilated and contained débris, casts and the outlines of crystals with surrounding leukocytic infiltration (Fig. 15). The lining cells were usually necrotic. In 1 case the tubules contained blood.

*Monkeys.** In the 3 monkeys receiving sulfathiazole for 14 days 1 showed a 15% drop in hemoglobin and all showed some degree of leukopenia. The urine and the non-protein nitrogen in the blood remained normal. There was no loss of weight. At autopsy apart from tuberculosis the only change was microscopic dilatation of the convoluted tubules with a few casts and débris in 2 animals.

In the animals receiving sulfathiazole for the longer period, 3 survived the 21 days. Of these 2 remained well throughout the period and the third showed some degree of leukopenia. At autopsy apart from tuberculosis the only changes were renal and resembled those in monkeys receiving sulfathiazole for 14 days. The fourth monkey in this group remained normal until the 17th day when albumin, red cells and crystals were found in the urine. Next day the monkey was dead. It showed 10% loss of weight. There were crystals in the bladder and a concretion impacted in the left ureter with dilatation of ureter and renal pelvis above. Both kidneys were filled with crystals which delineated the medullary rays and spotted the cortex. Microscopically, many tubules showed outlines of crystals (Fig. 19). Around such tubules and elsewhere were dense leukocytic infiltrations (Fig. 20).

All of the 3 animals receiving sulfapyridine for 14 days showed considerable leukopenia. The non-protein nitrogen of the blood rose in all, the highest figures being 260, 90 and 63 mg. per 100 cc., respectively. All 3 showed albumin and crystals in the urine and one in addition showed blood. The weight loss was 21%, 10% and 8% respectively. At autopsy, apart from tuberculosis, concretions were present in renal pelves, ureters or bladder (in 1 case in all three). Above the ureteral stones there were hydronephrosis and hydroureter (Fig. 17). Microscopically, tubules and glomerular capsules were dilated and contained albuminous fluid (Fig. 16), blood, casts and débris.

All of the 4 monkeys receiving sulfapyridine for 21 days showed leukopenia. In 1 the hemoglobin decreased 10%. In 3 the non-protein nitrogen was increased, the highest figures being 68, 62 and 108 mg. per 100 cc. Crystals and albumin appeared in the urine of all animals and blood in 2. The loss in weight was 6%, 12%, 14% and 24%. At autopsy one animal showed no changes in the gross and microscopically showed only dilatation of convoluted tubules with a few casts and débris. A second showed moderate bilateral hydroureter and microscopic changes somewhat more advanced than the first. In the other 2 there were ureteral concretions, hydroureter and hydronephrosis with pyelonephritis in 1 case. Microscopically, the tubules and glomerular capsules were dilated and contained albuminous fluid, casts and débris. There

* Since all monkeys were to be killed at the end of the experiment animals were chosen which appeared to have tuberculosis and most animals showed tuberculous lesions at autopsy.

were necrosis and other changes in the cells of the convoluted tubules. The pyelonephritis was represented by numerous abscesses in cortex and medulla (Fig. 18).

Discussion. Although sulfapyridine given as 1% or 2% of the diet did not appear to affect the mice adversely, microscopic examination showed that both drug concentrations had some effect on liver and kidneys. Similar slight changes in liver and kidneys were noted in mice given 1% sulfathiazole, and these animals in addition showed changes in the spleen resembling those described in certain other intoxications.[6] With 2% sulfathiazole diet, serious effects occurred. Deaths began as early as the third day and during the 28-day period of observation 77% of the animals died. These deaths seemed to be due chiefly to the effect on the genito-urinary system and great individual variation, perhaps in the degree of conjugation of the drug, was found. In half of the mice which survived the 28-day period little was seen in the kidney but the changes in spleen and liver resembled those seen in the animals that died. None of these changes were due to post-mortem autolysis since similar changes were found in surviving mice whose organs were fixed immediately. It should be noted that besides those renal changes due to the mechanical effect of the crystals or of concretions of these crystals, there appeared to be primary damage to the glomeruli as shown by hemorrhage at this point, and to the cytoplasm of the cells of the convoluted tubules.

In rats, in contrast to the mice, sulfathiazole was considerably less toxic than sulfapyridine. This was shown first by the growth curves (Chart 11). The amounts of drug consumed daily per kilo of initial weight did not differ significantly from one drug to the other. Only the genito-urinary tract showed lesions. Here sulfathiazole at either dose level produced very slight changes but both 0.5% and 1% sulfapyridine produced marked alterations. Recent experiments which have been performed in this laboratory suggest that the rate of metabolism of sulfathiazole in rats is so rapid and the sojourn of the drug in the blood so short that the blood level of rats receiving the 1% sulfathiazole diet will approximate that of rats receiving 0.5% sulfapyridine. This blood level of sulfathiazole, however, probably is not associated with genito-urinary lesions as frequently as an equal blood level of sulfapyridine. Metabolic studies are in progress to determine the total amount of drug passed through the kidneys at each dose of the two drugs. In the case of rats on sulfapyridine, as with mice on sulfathiazole, there appeared to be primary damage to the glomeruli and cells of the convoluted tubules quite distinct from those changes due to the mechanical effects of the crystals. It would appear that the different effect seen in mice and rats represents variation in species susceptibility. When the drugs are administered by mouth sulfapyridine is twice as toxic in rats as shown by the effect on the growth curve and more than twice

as toxic when the effect on the genito-urinary tract is considered. In the mice, on the other hand, when sulfathiazole is administered at levels above those necessary for therapeusis (*i. e.*, 2% in the diet), this drug produces marked genito-urinary changes and sulfapyridine produces none.

In monkeys the drugs were administered only once a day by stomach tube. It is realized that under these circumstances the blood concentration will be maintained at a more constant and higher level in the case of sulfapyridine than in that of sulfathiazole.[24] It is to be noted that the marked effect of either drug is on the genito-urinary tract and it would seem logical to suppose that the drug which was excreted more rapidly and in higher concentration through the kidneys, namely sulfathiazole, would produce the greatest effect or at least one not less than that of sulfapyridine. Such actually is not the case. In only 1 of 7 monkeys on sulfathiazole was there any effect on the genito-urinary tract and this was acute rather than chronic with steady rise in the non-protein nitrogen. With sulfapyridine, on the other hand, 6 out of 7 animals showed marked mechanical alterations in the genito-urinary tract and also primary renal damage. In every case this was accompanied by a rise in the non-protein nitrogen, often to high figures. The monkey dying from the effect of sulfathiazole and one of those on sulfapyridine showed widespread pyelonephritis. Unfortunately no cultures were taken but there is reason to believe that they would have proved sterile. These cases appeared to be merely an extension of what was seen in the rats and mice, namely an infiltration of leukocytes around any tubules or groups of tubules containing crystals of the drug. In addition to the genito-urinary changes it should be noted that 1 monkey on sulfathiazole (the animal which died) and 4 on sulfapyridine showed a loss of weight of greater than 10% during the experiment. In addition, 4 monkeys receiving sulfathiazole and all of those receiving sulfapyridine showed a steady decrease in the number of neutrophils in the blood which seemed to be significant.

Summary. 1. Sulfathiazole when given as 2% of the diet killed 77% of mice during a 4-week period and produced lesions chiefly in the spleen and genito-urinary tract. Sulfapyridine was not lethal and produced fewer pathologic changes.

2. In rats sulfapyridine was twice as toxic as sulfathiazole as shown both by the effect on the growth curve and by the lesions produced in the genito-urinary tract.

3. In monkeys receiving a single daily dose sulfapyridine was more toxic than sulfathiazole as shown by the lesions in the genito-urinary tract and, to a lesser extent, by loss of weight and leukopenia.

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PERIPHERAL NEUROPATHY AND TOXIC PSYCHOSIS WITH CONVULSIONS DUE TO SULFAMETHYLTHIAZOLE.

REPORT OF A CASE.

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THE toxic reactions caused by sulfamethylthiazole are similar in general to those of sulfanilamide and sulfapyridine. Thus, drug fever, dermatitis, granulocytopenia and hemolytic anemia have been encountered at Cleveland City Hospital following the use of sulfamethylthiazole. These reactions have not differed in any important detail from those described for sulfanilamide[2] and sulfapyridine.[1] Crystals of the drugs have frequently been found in the urine of patients receiving sulfamethylthiazole, as happens in patients receiving sulfapyridine,[4] and in several patients, hematuria has resulted.

Peripheral neuropathy, another complication which has been ascribed to sulfanilamide and certain of its allied compounds,[3,6,7] also has been encountered following the use of sulfamethylthiazole.[8] In one instance at Cleveland City Hospital the peripheral neuropathy was associated with a toxic psychosis. The character of the toxic reaction in this case was unusual enough to merit detailed consideration.

Case Report. E. K., a negro woman, aged 37, was admitted to Cleveland City Hospital, March 6, 1940. She had been in good health until March 1, when she had a severe chill followed by pain in the right side of the chest. Subsequently she became feverish and short of breath and coughed up sputum streaked with blood. She never had had convulsions and was not an alcoholic.

Examination showed an obese, acutely ill, moderately dyspneic negress. There was clinical and roentgenologic evidence of pneumonia involving the upper and middle lobes of the right lung. The temperature was 40.1° C. (104.2° F.), the pulse was 145 and the respiratory rate 45 per minute. Otherwise the physical examination was negative.

A Type XIV pneumococcus was found in both sputum and blood. The leukocytes numbered 9300 per c.mm., 82% being neutrophils. The red blood cell count was 4,000,000 and the hemoglobin was 10 gm. per 100 cc. Urinalysis revealed albumin, Grade 2. The slide test for syphilis (Kline) was positive; the Wassermann test was negative.

An initial dose of 4 gm. (60 gr.) of sulfamethylthiazole was given, with 1 or 2 gm. (15 or 30 gr.) every 4 hours thereafter. See Chart 1 for the exact amounts.

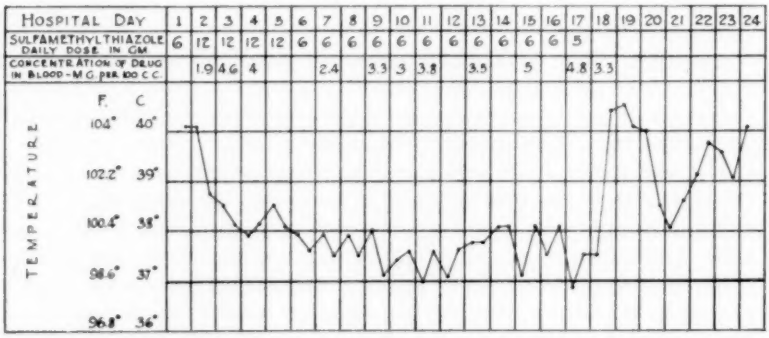

CHART 1.—Doses of sulfamethylthiazole, concentration of the drug in the blood, and temperature.

Four hours after admission, reëxamination showed the cardiac mechanism to be auricular fibrillation. Digitalis was given. In 36 hours the mechanism reverted to normal, and the use of digitalis was discontinued.

The patient improved slowly. There was no growth in the blood cultures taken on the second, third, fourth and sixth hospital days. The temperature fell gradually by lysis but did not become normal and since resolution of the pneumonic process was occurring slowly, chemotherapy was continued. The blood level of sulfamethylthiazole averaged 3.6 mg. per 100 cc. of blood (Chart 1).

Despite the fact that thiamine chloride was being administered intravenously and intramuscularly, on the seventeenth hospital day there was definite tenderness and hyperesthesia of the legs, which was considered to be indicative of early peripheral neuropathy. The use of sulfamethylthiazole was stopped immediately. The patient was oöperative and mentally clear at this time.

The next morning the patient had two generalized convulsions, each of which lasted about 3 minutes, following which she was unresponsive, agitated, resistive, delirious and required restraint and intravenous sedation. As far as could be determined, neurologic and general physical examination was negative. A lumbar puncture was done and the spinal

fluid pressure was found to be normal. The fluid was clear and contained no cells. The Wassermann reaction of the spinal fluid was negative. That afternoon the temperature rose to 40° C. (104° F.) and her condition was poor.

During the following 3 days the patient had 12 generalized convulsions. She was unresponsive, stuporous and in a critical condition. No abnormal physical or neurologic findings could be demonstrated. A film of the chest showed almost complete resolution of the pneumonic process. Another lumbar puncture was done and again the spinal fluid was found to be normal. The blood urea nitrogen was 32.6 mg. per 100 cc. of blood. The white blood cell count was 12,000 and the red blood cell count was 4,200,000. Urinalysis was negative except for a small amount of albumin. The patient became increasingly stuporous during the next 2 days and died on March 29, on the twenty-fourth hospital day.

Autopsy. (No. 13167, performed by Dr. K. H. Kemp, 1½ hours after death.) The lungs showed no evidence of pneumonia. There was bronchiectasis and bronchitis in the upper lobe of the right lung. The alveoli of the middle and lower lobes of the right lung contained blood, apparently of rather recent origin. There were considerable edema and a few small areas of hemorrhage in the left lung. The heart was normal. The abdominal viscera showed severe cloudy swelling. The brain was normal grossly and microscopically.

Comment. The clinical and autopsy findings adequately establish the fact that this patient died of a toxic psychosis. Only two drugs, thiamine chloride and sulfamethylthiazole, need to be considered as possible causative agents. Thiamine chloride cannot be incriminated, as massive doses of this drug have not caused toxic symptoms. On the other hand, it is reasonable to ascribe the toxic reaction to sulfamethylthiazole, especially since the sulfanilamide radicle has been known to cause toxic psychoses. Convulsions caused by sulfanilamide have not been reported[5] and in this respect the case is noteworthy. The peripheral neuropathy can be attributed to no other cause than the sulfamethylthiazole and is additional evidence of the toxicity of the drug to this particular patient.

Summary. Experience at Cleveland City Hospital indicates that in general the toxic reactions of sulfamethylthiazole resemble those previously described for sulfanilamide and its allied compounds. One case at Cleveland City Hospital has been exceptional and has demonstrated a hitherto unreported reaction. In this instance peripheral neuropathy appeared while the patient was receiving sulfamethylthiazole. The use of the drug was stopped but shortly thereafter the patient suffered a violent toxic psychosis with convulsions and died.

Sulfamethylthiazole was available for study through coöperation with the Medical Research Division of the Winthrop Chemical Company.

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SULPHAPYRIDINE IN THE TREATMENT OF GONOCOCCAL INFECTIONS AFTER SULPHANILAMIDE FAILURE.

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THE therapy of gonococcal infections has undergone great change and improvement since the introduction of the sulphanilamide class of drugs. The relative merits of the various modifications, however, still remain to be evaluated for different diseases.

In a previous study[1] of the hospital treatment of gonorrhea with sulphanilamide, we found that it was promptly effective in 76% of 298 patients. The failure patients we considered under three different groups: 1, Those who did not respond to sulphanilamide in adequate doses; 2, those inadequately treated as out-patients; 3, self treatment from irresponsible drug stores.

Groups 2 and 3 received an adequate course of sulphanilamide therapy after admission. However, it has been our experience that these patients are not responsive to further sulphanilamide therapy. Certain few individuals appear to change and excrete this drug too rapidly to secure clinical effect. Prolonged inadequate dosage appears to raise the resistance of the patient's infection towards the drug. Several theories as to the site and manner of action of the sulphanilamide chemicals have been expounded in the literature. It is not the purpose of this report to discuss them.

To evaluate the allied drug sulphapyridine in the sulphanilamide failure patients, 100 seafaring men, between the ages of 20 and 40 in good physical condition were selected. All of these patients had been adequately treated with sulphanilamide.

Method. The initial dose of sulphapyridine was 1 gm. every 4 hours day and night for 2 days, then ½ gm. every 4 hours day and night for 4 to 8 days, according to the patient's response.

The average number of days of treatment was 7. We did not correlate the concentration of the drug in the blood with the dosage in this investigation.

The fluid intake was limited to 1 quart per 24 hours. During the summer months 1½ quarts were allowed. When laxatives were necessary enemata or cascara sagrada were used.

The results of this treatment were 75% of cures in 100 patients who had failed upon sulphanilamide. In the successful cases the urethral discharge disappeared within 5 days after administration of sulphapyridine.

The criteria of cure was as follows: After the disappearance of the urethral discharge and the urine was clear by the 2-glass test.

the meatus was cleansed with soap and water. A curved sound was passed into the bladder. The pendulous portion of the urethra was massaged on the sound. The sound was withdrawn and the prostate was massaged. The urethro-prostatic secretion was examined by smear and culture.

If found to be negative for gonococci, the entire procedure was repeated after a 2-day interval. Three such negative reports were obtained before the patient's release.

The sounds were lubricated with sterile tragacanth jelly free of preservatives.

A slight serous "morning drop," a few fine shreds when both glasses of urine were clear were not construed as indicating failure if the other criteria of cure were present.

We are now using this drug for the routine hospital treatment of the gonococcal infections.

It has been more agreeable for the patients to take. The cyanosis is less. However, the nausea and malaise are quite constant for each patient. Numerous crystals are present in the urine, also red and white cells, and small amounts of albumin while the patient is under treatment. These urinary findings clear up after treatment without residual effects in our experience. We have encountered no alarming symptoms among many patients treated, exclusive of the above group of sulphanilamide failures. One individual, not in this group, developed a mild granulocytic leukopenia. He recovered promptly after the discontinuance of the drug.

However, we reiterate the opinion expressed in our article on sulphanilamide therapy, that this class of chemicals is not without danger if prescribed to patients who are not in the hospital or who are not under daily clinical observation.

The toxic symptoms of nausea and malaise may cause certain out-patients to discontinue the recommended amounts of drug, and thus result in failure of treatment.

Patients under therapy with sulphapyridine or sulphanilamide class of drugs should receive frequent blood counts to guard against granulocytosis.

Conclusions. 1. One hundred patients who had failed of cure on sulphanilamide therapy were treated with sulphapyridine.

2. Of these, 75 were cured in an average of 7 days.

3. Inadequate treatment with sulphanilamide raises the resistance of the patients' infection towards this drug.

4. Sulphapyridine has proved superior to sulphanilamide in the treatment of gonorrhea in our experience.

5. It is preferable to treat patients in the hospital to insure against untoward toxic effects and to assure correct and adequate dosage.

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TREATMENT OF THE FALCIPARUM MALARIA OF DRUG ADDICTS.

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FALCIPARUM malaria is endemic in the drug addict population of New York City.[1] Since 1933, more than 200 such cases have been admitted to our wards in Bellevue Hospital. Epidemiologic,[2a] clinical,[2b] and laboratory[3] studies of these patients who have presented every clinical variety of falciparum malaria, have been reported elsewhere. Since the practise leading to the transmission of this disease—the common use of an apparatus for the administration of heroin intravenously—is becoming increasingly popular among drug addicts, it is likely that endemic foci will appear also in other cities. It seems desirable, therefore, to report our tried and satisfactory routine for the treatment of its various clinical forms.

In the early years of our experience with this disease, the mortality exceeded 50%. This was due, we now believe, to the following circumstances: first, that the patients presented themselves for treatment late in the course of the disease; second, that the medical staff often failed to establish the diagnosis within a few hours of the patient's admission; third, that the staff was not familiar with an effective method of treating the cerebral form of this disease. In recent years the mortality has fallen to about 10%. This has resulted, we believe, from the reversal of the above conditions. The object of this paper, therefore, is to describe that form of treatment which has been most effective in producing rapid recovery from the disease with the shortest possible period of hospitalization, reducing to a minimum the likelihood of relapse, and preventing the patient from becoming a public health menace. These objectives were accomplished by a combination of specific chemotherapy and supportive measures.

Chemotherapy consists of:

1. The destruction of asexual parasites, responsible for the disease in man, by the administration of quinine dihydrochloride intravenously, or atabrine orally, or both. Quinine dihydrochloride is given intravenously as an emergency measure, to establish immediately a high concentration of a plasmodicide in the blood of patients

showing involvement of the nervous system, or when vomiting or diarrhea exists. Atabrine is given after a satisfactory response to the emergency treatment with intravenous quinine has occurred. In the less severely ill patients, who do not exhibit cerebral or gastrointestinal signs or symptoms, atabrine is given in the first place, the intravenous therapy being omitted.

2. The destruction of sexual parasites, responsible for transmission of the disease via the mosquito, by the administration of plasmochin. This drug is given only as a gametocide after a clinical response to quinine and atabrine has been obtained, or to symptomless carriers of gametocytes.

Supportive therapy consists of combatting shock, dehydration, anemia, and hypoproteinemia by the restoration of fluids, salt, blood, and plasma proteins.

The application of these therapeutic principles to the various clinical forms of falciparum malaria in the drug addict will be described separately for each one.

Cerebral Form. In the presence of cerebral involvement as manifested by clouding of consciousness, severe headache, convulsions, or frank neurologic signs (such as pyramidal tract or posterior column signs, ocular palsies, rigidities, and other encephalopathic manifestations), quinine dihydrochloride is administered intravenously, in doses of 0.6 gm. in 10 cc. of physiologic saline solution, every 3 to 4 hours for at least 24 hours during the day and night. No effort is made to give food or drugs by mouth or stomach tube. From 2000 to 5000 cc. of fluids per day is given parenterally in the form of a 5% solution of glucose in physiologic saline, to which 10 mg. of thiamin chloride is added as a prophylaxis against vitamin B_1 deficiency. This is continued until urine specimens, obtained every 8 hours by catheter, are free from acetone and have a specific gravity of less than 1.015. If there is severe anemia or jaundice, or if the urine is bright red or brown and contains oxyhemoglobin or methemoglobin; if shock is present, or if the plasma proteins are low, 500 cc. of whole citrated blood is given as an infusion. This is repeated within 12 to 24 hours if evidence of marked hemolysis persists. If there is marked cyanosis, oxygen is administered by nasal catheter or mask. If there is no remission in the depth of the coma within 8 hours, 50 cc. of spinal fluid is withdrawn. Simultaneously, 50 cc. of a 50% glucose solution and 1 cc. of 1 to 10,000 adrenalin are given intravenously. This procedure may be repeated in 6 hours if no improvement in the clouding of consciousness is apparent. Dramatic recovery from severe coma or convulsions is brought about occasionally by this expedient.

When clinical improvement is noted, usually on the second day, the interval between intravenous injections of 0.6 gm. of quinine, is lengthened to 6 hours. If improvement continues, the intervals are lengthened to 8 hours on the third day, and to 12 hours on the fourth

day. The intravenous administration of quinine dihydrochloride is continued on the third and fourth days even though the patient looks and feels well and is able to take nourishment by mouth; it is limited to 4 days, however, even in severely ill patients.

As soon as the patient can take fluids by mouth he is encouraged to drink fruit juices and milk at frequent intervals. This nourishment is supplemented by semi-solid foods as soon as possible. No drugs are given by mouth and enemas are given every day. In order to avoid the intestinal or nervous complications of drug withdrawal, no attempt is made to withhold heroin or morphine, until the patient is convalescing from the falciparum malaria. The efficacy of treatment is judged, during this acute phase, by disappearance of the cerebral manifestations rather than by the temperature or the number of parasites found in the blood.

The next phase of treatment consists of giving atabrine, by mouth, in doses of 0.1 gm. three times daily for 7 days. At this time, when the patient is usually convalescent, a diet rich in calories and vitamins, supplemented by injections of liver parenterally, ferrous sulphate, and vitamin concentrates, is prescribed, and drug withdrawal is started. If, after 7 days of atabrine, gametocytes are found in the peripheral blood, plasmochin is given for 4 days in doses of 1 tablet of 0.02 gm. three times daily. The specific treatment for malaria is now ended. When heroin withdrawal is completed, the patient is instructed to return to a follow-up clinic for observation.

If, when admitted, the patient presents only a few or no neurologic signs, and only mild mental symptoms, such as moderate confusion, dullness, and apathy, the treatment after the first 24 hours need not be so vigorous as outlined. On the second day quinine may be given intravenously only every 8 hours and the administration of atabrine may be started on the third day, and continued for 7 days. In other respects the treatment is as outlined.

Severe Gastro-intestinal Involvement. A moderate number of individuals show evidence of severe intestinal localization of the infection in the form of intractable vomiting, often associated with jaundice, or severe diarrhea. In such cases the patient's stomach is lavaged and a purge given immediately following his admission to the ward, after which he is permitted to have nothing but cracked ice by mouth. Enemas are administered daily. During the first 2 or 3 days quinine dihydrochloride is administered intravenously and fluids parenterally as in the cerebral form. By the end of the second or third day the gastro-intestinal symptoms have, as a rule, disappeared. At this time atabrine by mouth is substituted for the quinine for a full week, and a low residue diet is prescribed and gradually increased in quantity. If gametocytes are present in the blood, plasmochin is given before the patient is discharged from the hospital.

Blackwater Fever. This syndrome, the result of intravascular corpuscular hemolysis, is characterized, in its early stage by malaise, chills, abdominal or loin pain, vomiting, shock, and dark red, brown, or black urine; later by fever, azotemia, oliguria to anuria, and jaundice. The signs and symptoms depend on the extent of the initial hemolysis and on whether the process recurs. Although blackwater fever is rare in New York, we have seen 2 cases in our series of drug addicts having falciparum malaria.

Treatment consists of the administration of whole blood, by means of a continuous drip infusion, until the emergency of shock and severe anoxemia has been overcome. This method can be employed only if large amounts of blood (1,000 to 5,000 cc.) are available. Otherwise direct transfusions of blood and infusions of 5% glucose in physiologic saline solution must be resorted to. Quinine is not given, but if numerous parasites are present in the peripheral blood, atabrine may be given in the dosage previously described. As a rule, however, this phase of the treatment may be postponed until the patient has recovered from the blackwater fever.

Simple Malaria, Latent Cases, Gametocyte Carriers. Drug addicts having malaria uncomplicated by severe nervous system or gastrointestinal involvement, or symptomless addicts discovered harboring asexual forms of plasmodia, are treated by the administration of atabrine in doses of 0.1 gm. by mouth three times daily for 7 days. At the termination of this period 0.01 gm. of plasmochin is given three times daily until gametocytes are no longer found in the circulating blood. The patient is kept at bed rest, intake of fluids is forced and a diet rich in calories and vitamins is given. Bowel hygiene should not be neglected. If the patient is anemic 0.3 gm. of ferrous sulphate is given three times daily. If, in a routine examination of a drug addict, only gametocytes of *P. falciparum* are found in the blood, 0.01 gm. of plasmochin is given three times daily until they disappear.

Relapse and Reinfection. Subsequent to their treatment and discharge from the hospital, several patients returned within a fairly short time showing symptoms of malaria, and parasites in their blood. It is difficult to accept the statements of drug addicts, but in 2 of our patients it seemed fairly certain that there had been no re-exposure. One of these had been transferred to another ward after his recovery from the malaria, and the relapse occurred less than 2 weeks after termination of the original treatment. This patient, however, had received only quinine. The second individual had been sent to a convalescent home in the country, and his relapse occurred within 3 weeks. This patient had been treated fully with quinine, atabrine, and plasmochin, and was free of malarial symptoms and parasites, and of evident symptoms of heroin addiction, when he left the hospital. There were no other known addicts at the country home where the patient was sent, and it seems fairly certain that this patient was not exposed to reinfection naturally or artificially. This case is of particular interest in view of the evi-

dence that the relapse rate following atabrine is less than that for quinine; and further, because relapse occurred in spite of intensive therapy. These cases emphasize the desirability of post-convalescent observation.

Many drug addicts resort to intravenous heroin administration after their recovery and discharge from the hospital. Some of our patients who returned with a second attack of acute malaria, admitted the common use of syringes with other addicts during the interval. As the immunity to malaria is extremely short, reinfection was undoubtedly the mechanism accounting for the recurrence of malaria in these cases. Ironically, a few of these addicts died during the second episode of the disease.

Effects of Treatment. It is difficult to evaluate the effects of treatment in falciparum malaria among drug addicts. Lower mortality rates in recent years may be ascribed to the fact that addicts as well as hospital physicians know of the disease. As a result, patients present themselves early for treatment often announcing the diagnosis. Seldom is the diagnosis missed even in the admitting office. Treatment, therefore, is instituted promptly, and blood smears are taken only to confirm the diagnosis. In spite of these factors there were six deaths in 35 cases admitted to our services during 1938. In 1939, however, there were only two deaths in 50 acute cases. This is still a high death rate, but compares favorably with the 50 to 75% mortality experienced during the first years after the cerebral form of the disease was recognized.

There is no intention of correlating mortality and treatment. We merely wish to point out that the disease, as it occurs in these addicts is a serious one, and all efforts should be directed towards early and intensive therapy. If because of inexperience or lack of facilities a diagnosis of malaria cannot be confirmed in an acutely ill drug addict, specific therapy should be given. Likewise in acutely ill patients having the telltale discolorations of drug administration over the antecubital veins, this diagnosis should be seriously considered and specific antimalarial therapy given even in the absence of a history of addiction. We do not believe that specific therapy will harm the patient, and it should not interfere with other diagnostic or therapeutic measures if the disease should not be malaria. By this means fatal experiences resulting from failure of diagnosis may be avoided.

In New York City the Health Department has no jurisdiction over the activities of drug addicts having malaria. Since we have successfully infected anopheline mosquitoes with the malaria from the blood of drug addicts who had recovered from the disease, it is obviously desirable to have such control in order to enforce effective treatment as drug addicts must always be considered a potential focus for a malarial epidemic in any community where suitable mosquitoes are abundant. For the same reason it is essential as a public health measure, in a community where suitable anophe-

line mosquitoes and drug addicts are present, to include an effective gametocidal drug in the treatment.

Summary and Conclusions. 1. Falciparum malaria is endemic in New York City among drug addicts practising the common use of a hypodermic apparatus for the administration of heroin intravenously.

2. The mortality is very high unless effective treatment is given soon after admission to the hospital.

3. In the presence of nervous system or gastro-intestinal involvement chemotherapy should be limited during the acute phase to the administration of quinine dihydrochloride intravenously. When the emergency phase has passed, atabrine should be given orally. To less severely ill patients, or to symptomless carriers of asexual parasites, atabrine alone should be given. Plasmochin should be given as a gametocide to all patients before they are discharged from the hospital. Supportive therapy should include the restoration of fluids, salt, blood, and plasma proteins.

4. A routine for the treatment of the various clinical forms of falciparum malaria in the drug addict is outlined.

5. Drug addicts presenting acute obscure syndromes who show signs of having taken heroin intravenously should be treated for malaria until another diagnosis can be established.

6. Heroin addicts having falciparum malaria should be under the legal jurisdiction of the Health Department to safeguard the health of the community.

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β METHYLCHOLINE URETHANE.

ITS ACTION IN VARIOUS NORMAL AND ABNORMAL CONDITIONS, ESPECIALLY POSTOPERATIVE URINARY RETENTION.*

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CERTAIN of the derivatives of choline are among the most active drugs known to man and their therapeutic possibilities are just being realized. Those used as medicaments have an action similar

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to the effects which follow stimulation of parasympathetic nerves.[4,15a] Therefore slowing of the heart, peripheral vasodilatation, increased gastro-intestinal activity, increased bladder tone, sweating, salivation and bronchoconstriction are easily demonstrated in animal experiments after giving these drugs.[3] With certain modifications these effects are also found in man and they can be prevented or abolished by atropine.[18] In addition, certain of these drugs have an action like nicotine which is not antagonized by atropine.[4,15a,17c] This action, demonstrated in animal preparations by a rise of blood pressure after atropine, and by certain muscular contractions, is less conspicuous than the parasympathetic effects but, of no known clinical utility, it is certainly undesirable.

Several drugs of the choline series have been used as medicaments. Acetyl choline, the first discovered, is of great scientific interest,[4] but it has made a poor medicament as it is destroyed in the body with great rapidity. It has a strong nicotine-like action in addition to the characteristic parasympathetic effects.[4,15a]

Acetyl β methyl choline (mecholyl) lacks the nicotine-like action and, though not stable, it is far less rapidly destroyed than acetyl choline.[15a] After subcutaneous injection in man intense effects come on rapidly and pass off in a short while.[18] Given by mouth, the action is very mild and the dose required 10 to 30 times the subcutaneous.[18] This drug has been used to arrest paroxysmal tachycardia,[17a,b] in peripheral vascular disease,[10,17a] and for effects on the bladder.

Carbaminoylcholine (doryl) was the first stable choline derivative synthesized. A very active drug of minute dosage, it has a strong nicotine-like action.[6] It has been chiefly used in the treatment of postoperative urinary retention, in peripheral vascular disease, and for its gastro-intestinal action in veterinary medicine.[17c]

Carbaminoyl-β-methylcholine, also properly called β methylcholine urethane (B.M.C.U.) was synthesized in 1935, by Major,* at the suggestion of Simonart,[16b] who from theoretical considerations had anticipated that such a compound would resemble doryl but lack the nicotine-like effect. This expectation proved to be justified for the drug is stable and the nicotine-like effects are very feeble.[16a,b] Its other pharmacologic effects, tested in animal preparations, resemble the parasympathetic-like action of the other active choline derivates.[5a,b] It is weaker than doryl, the subcutaneous dose for man being about 10 times greater, but also less toxic, the minimal lethal dose for mice, rabbits, and cats, being about 30 times greater than that of doryl.[9,16b] In animal preparations it causes marked intestinal stimulation in doses which have no effect on blood pressure.[17b,20]

Doryl has been used in this clinic since 1934.[17c] During this experience we occasionally encountered uncomfortable side effects not rapidly relieved by atropine, a fact which made us suspect that

* The drug was supplied through the courtesy of Merck & Co., Inc., Rahway, N. J.

they were due to the nicotine-like effects of the drug. Therefore, we resolved to try B.M.C.U., and this paper is a report of our experiences.

The action of B.M.C.U. has been studied both in healthy volunteers and in patients; over 150 individuals have received it. In postoperative urinary retention the drug has caused prompt emptying of the bladder in many cases. In neurologic conditions its administration has frequently been followed by the replacement of dribbling by automatic emptying of the bladder. We have also employed the drug with benefit in abdominal distention, intestinal atony in children, and peripheral vascular disease.

During this experience we have encountered very few uncomfortable and no dangerous side effects. It is this freedom from untoward action, rather than an increased therapeutic effectiveness, which has made us believe the drug to be superior to doryl.

Action on Normal Persons. *Method of Administration.* We have used the chloride of β methylcholine urethane. It is not hydroscopic. Two milligram tablets have been used most frequently, and it was convenient to have 4 mg. and 6 mg. tablets also. Oral administration presented no difficulty. Local irritation after subcutaneous injection was slight. Intravenous injection was not attempted.

The Action After Subcutaneous Injection. Twenty-two healthy medical students volunteered to receive the drug and were given subcutaneous doses ranging from 2 to 10 mg. The subjects lay on a couch for a period of at least 15 minutes before the injection and remained there for the duration of the observations. The routine observations were made by Starr or by students working under his direction. All subjects were ignorant both of the type of drug and the dose they were receiving, and some, serving as controls, received injections of water.

The effects of B.M.C.U., summarized in Table 1, came on gradually. If there was any detectable effect on the circulation it appeared in from 5 to 10 minutes. Slight sweating and salivation followed. The gastro-intestinal and bladder effects appeared last, reaching their maximum between 20 and 30 minutes after the injection. After this time all evidence of action gradually diminished but 3 subjects defecated, contrary to their usual habit, between 3 and 5 hours after receiving the drug.

After doses of from 2 to 3 mg., the effects were all very slight, the subject often being at a loss to decide whether he had received an active drug for about 20 minutes. Then the sensation of increased peristalsis and the borborygmi, clearly audible to the listening observers, were perceived.

After doses of from 4 to 6 mg. most subjects were unconscious of any effects on the circulation. The observers noted a flush in less than half the cases and the changes of blood pressure and pulse rate were usually too small to be attributed to the drug. However,

slight salivation was regularly noted and increased sweating of the palms could often be demonstrated. Again increased peristalsis was conspicuous and, in over half the cases, this was accompanied by a definite desire to void so intense that it was called painful in 3 cases.

TABLE 1.—EFFECT OF SUBCUTANEOUS INJECTIONS OF β METHYLCHOLINE URETHANE ON NORMAL YOUNG ADULT MALES.

	Subcutaneous doses.		
	2 to 3 mg.	4 to 6 mg.	7 to 10 mg.
Number of cases receiving the dosage given above	5	12	5
Number of subjects who showed effects given below.			
Systolic blood pressure change:			
Less than 5 mm. Hg	2	9	2
Fell 5 to 10 mm. Hg	3	1	2
Fell over 10 mm. Hg	..	..	1
Rose 5 to 10 mm. Hg	..	1	
Rose over 10 mm. Hg	..	1	
Diastolic blood pressure change:			
Less than 5 mm. Hg	5	8	2
Fell 5 to 10 mm. Hg	..	3	2
Fell over 10 mm. Hg	..	..	1
Rose 5 to 10 mm. Hg	..	1	
Pulse rate:			
Change less than 5	4	8	1
Increased 5 to 10	..	1	1
Increase 10 to 15	..	2	2
Decrease 5 to 10	1	1	
Decrease over 10	..	..	1
Flush	3	6	2
Sensation of warmth (early)	2	2	2
Sensation of cold (later)	..	2	4
Sweating	1	6	5
Salivation	4	12	5
Lachrymation	..	..	1
Increased peristalsis	5	10	6
Bowels moved	2	1	2
Abdominal cramps	..	..	2
Nausea	..	..	2
Epigastric discomfort	..	1	
Desire to urinate	..	7	2
Pain referred to bladder or urethra	..	3	1

Doses of from 7 to 10 mg. were followed by only slight effects on the circulation. The flush was seen in only 2 of the 5 cases receiving this dose. Sweating and salivation occurred in all 5 cases but they were not excessive. Again the gastro-intestinal effects were conspicuous: 2 cases had abdominal cramps, 2 were nauseated, and it was the uncomfortable gastro-intestinal manifestations which caused us to give atropine in 3 instances. The bladder manifestations were prominent in only 2 of the 5 cases; pain referred to the penis was reported by 1 of these.

In subjects with full bladders the desire to void regularly followed the administration of the drug, but if the bladder had recently been emptied, this sensation did not occur.

Effect on the Cardiac Output. Seven normal subjects were given the drug while resting on the ballistocardiogram[19] and their cardiac

output was estimated before and after its administration. The results are given in Table 2. In most cases the effects on the circulation were not greater than the changes which occur after injections

TABLE 2.—EFFECT OF SUBCUTANEOUS INJECTIONS OF β METHYLCHOLINE URETHANE ON THE CIRCULATION.

Time.	Subject.	Dose (mg.).	Heart rate (per min.).	Blood pressure (mm. Hg).	Cardiac output (cc. per min. per lb.).	Remarks.
10 50	G. A.	..	68	110/70	21	Normal.
11 00		3				
11 06			65	110/70	22	
11 20			63	112/68	23	Salivation?
11 33			64	112/80	21	Face feels hot.
11 00	H. E.	..	88	112/94	28	Normal.
11 04		4				
11 20			80	110/78	28	Sweat only in palms; desire to void; peristalsis.
11 32			73	106/87	28	Same.
11 30	J. McC.	..	71	110/75	22	
11 35		4				
11 50			68	110/75	21	Peristaltic sounds increased.
11 55	R. L.	..	70	115/88	25	
12 00		6				
12 13			75	123/85	26	
12 23			72	114/74	28	Slight salivation and sweating.
12 33			78	108/68	26	Peristalsis increased.
11 38	T. G.	..	74	125/90	24	Normal.
11 42		6				
11 50			60	122/90	21	Sinus arrhyth.; peristalsis ++.
12 02			74	122/84	24	Sweating a little; salivating; peristalsis ++; desire to void.
10 30	R. W.	..	65	124/70	20	
10 35		6				
10 40			62	118/66	21	
10 52			60	110/66	22	Peristalsis increased.
11 26	S. P.	..	70	114/80	24	Normal.
11 27		8				
11 34			54	87/60	17	Feels weak; face pale.
11 45			64	104/70	22	Salivating a little; peristalsis +; face not pale.
11 58			64	106/72	22	Same.

of inert solutions, but a significant diminution of cardiac output accompanied marked slowing of the pulse in 2 instances.

Action After Oral Administration. Twenty patients received B.M.C.U. by mouth in divided doses which ranged from 2 to 24 mg.

daily. The great majority of these cases did not notice any side effects at all. In no case was any noteworthy effect on the pulse rate or blood pressure detected by the observers. Salivation was never complained of, sweating was noted only occasionally after the larger doses. The development of diarrhea made us reduce the dose on 2 occasions.

Routine hospital blood counts and urinalysis taken during the administration of the drug showed nothing that could be attributed to it. Electrocardiograms taken in 3 persons under its influence were likewise negative.

It is obvious that B.M.C.U., taken by mouth in suitable dosage, produces almost no uncomfortable side effects. While we obtained some evidence suggesting cumulative effects, it was never striking and most patients tolerated a constant daily dose without difficulty.

Therapeutic Use of the Drug. *In Postoperative Urinary Retention.* This complication is seen most often in operations on the lower abdomen or on the perineum and it may be looked upon as a reflex depression of the parasympathetic nerves which stimulate the detrusor muscles of the bladder. In its treatment the use of the drug was withheld in all cases until it was evident that catheterization would have to be performed. In a few cases, however, just before the drug was given, the patient voided. This is one of the difficulties encountered in evaluating the functions of any drug in this condition.

B.M.C.U. was administered hypodermically in 2 mg. doses, the patient being previously arranged so that voiding could take place at once if bladder contractions stimulated urination. If voiding did not occur within 20 minutes to half an hour, the same dose was repeated. At times a third dose, and even a fourth, was given at intervals of about 15 to 30 minutes. Untoward reactions were noted in only 1 patient who felt somewhat faint after the administration of the drug. This was relieved by the administration of a hypodermic of 1/150 gr. atropine. In 2 other patients, definite contractions of the bladder with pain were experienced but voiding did not occur. In 1 patient, following a resection of the rectum for carcinoma, it was necessary to catheterize the patient 4 times daily for 11 days after operation. On the 12th day, a supply of B.M.C.U. was obtained. The patient voided after the second dose of the drug and did not require catheterization after that.

The sum of the results is given in Table 3. In all there were 122 attempts to relieve postoperative urinary retention. In this group, voiding followed the use of the drug in 82 cases (68%). In 40 cases, the drug failed to produce urination. In the successful cases, 37 voided after the first dose of the drug, 35 after the second dose, 8 after the third, and 2 after the fourth dose. It is apparent that if the drug is to be effective it will usually act after the first or second dose. After the third dose, there are more failures than successes.

In a few cases retention, once relieved by the drug, recurred and

it was necessary to give B.M.C.U. for several days in order to stimulate urination. There did not seem to be any untoward effects from this repeated use of the drug and when it was effective on one occasion, it was usually effective on subsequent occasions.

TABLE 3.—β METHYLCHOLINE URETHANE IN POSTOPERATIVE URINARY RETENTION. Given in doses of 2 mg. s.c., usually repeated in 20 to 30 minutes p.r.n.

Type of operation.	No. of success.	No. of failures.
Appendectomies	29	8
Herniorrhaphies	26	10
Hemorrhoidectomies	5	4
Upper abdominal	9	6
Colon	2	2
Genito-urinary	3	1
Others	8	9
Totals	82	40

In Other Types of Urinary Retention. In animal experiments parasympathetic denervation of any organ enhances the action of acetyl choline upon it.[4] Hence one might expect unusually vigorous action of choline derivatives in certain neurologic conditions. However, while we have seen the administration of choline derivatives most successful in cases of urinary retention in neurogenic bladders, the dose required did not differ from that which was successful in other types of disease.

B.M.C.U. has been used in two ways in these cases. First, subcutaneous injections can be used to cause a full bladder to empty; second, given by mouth the drug usually prevents over-distention and results in automatic emptying at a fairly definite content.

For example, a man of 68 years having had a chordotomy to relieve the pain of inoperable rectal carcinoma was entirely unable to void. Six milligrams B.M.C.U. subcutaneously failed, but 10 mg. regularly emptied the bladder about 10 minutes after the injection without any uncomfortable side effects. This dose was given every 6 hours for the following 3 weeks and was successful in every instance. At the end of this time the bladder began to empty automatically and the drug was successfully withdrawn.

In another case, a man of 26 with retention after a laminectomy, 8 mg. subcutaneously caused sweating, salivation, and abdominal cramps but he voided only 50 cc. and 750 cc. was then obtained by catheter. A very similar experience was repeated 4 times during the next 4 weeks when attempts were made to discontinue the continuous drainage. At the end of this time 6 mg. t.i.d. by mouth for 2 days, giving no side effects, was followed by the development of an automatic bladder emptying at about 300 cc.

Experience with two children who suffered from painful over-distention of the bladder without known cause, 3 cases in which the over-distention complicated acute infections, 5 cases of prolonged postoperative retention, and many neurologic cases suggests that,

in the absence of organic obstruction, over-distention can be usually prevented by the administration of choline derivatives given by mouth. For this purpose we now employ 2 mg. B.M.C.U. t.i.d. and if, after 2 days' trial, this is unsuccessful we increase the dose until either the desired effect is achieved or uncomfortable side effects become prominent. If uncomfortable symptoms appear, atropine will relieve the patient very rapidly.

We have made no study of the effects of B.M.C.U. in post-partum retention of urine, but we have frequently supplied the drug to friends in contact with such cases and know of many instances in which it was used successfully.

Gastro-intestinal Effects. We have used B.M.C.U. 10 times in cases of abdominal distention and occasionally it has been extremely successful. We can cite such an experience in a case markedly distended for 1 week during the passage of a renal calculus. During the preceding 3 days he had received at appropriate intervals a rectal tube repeatedly, 3 flaxseed poultices, castor oil, 2 milk and molasses enemas, 5 ampules of pitressin, and 1000 cc. of 5% glucose in physiologic saline solution, without relief. Then, with a rectal tube in place, the administration of 4 mg. of B.M.C.U. subcutaneously was followed by markedly increased peristaltic sounds, abdominal cramps, and the expulsion of large amounts of flatus 12 minutes later. Twenty-five minutes after the drug the abdomen was soft for the first time in a week.

Unfortunately, dramatic results of this type were secured in only 2 of 10 trials. The drug regularly increased the peristaltic sounds in such cases and usually caused cramps, but the expulsion of flatus did not follow in 5 of the 10 instances in which the drug was used alone. However, the insertion of a rectal tube or the giving of an enema during the drug's action produced the desired result on 3 occasions.

In summary, we have seen B.M.C.U. fail where pitressin, given later, succeeded, and we have seen it succeed after many other measures had failed. Sometimes extremely successful, in other instances its effect is disappointing, and we believe that a similar uncertainty exists for all the remedies regularly used in the treatment of distention. The advantage of this drug over most of the others employed in this condition is that any untoward effects could be entirely overcome by its antidote atropine.

In 2 cases, remarkably similar, the laxative action of the drug was successfully employed.

CASE 1.—L. D., a colored boy of 12, a patient on Dr. Gitting's service, had been well till the age of 6. Since that time he has had 6 admissions to the hospital because of extreme constipation. He often went a week without defecation and the abdomen was usually full of fecal masses. The child was subnormal mentally and had a B. M. R. at times subnormal, −20% on 2 occasions, within normal limits on 2 more occasions. Roentgen ray disclosed a greatly dilated sigmoid. A large number of laxatives and

enemas, alone and in combination, had failed to produce a regular habit and thyroid had been given unsuccessfully on various occasions. B.M.C.U. was given in doses of 2 mg. t.i.d., later 4 mg. t.i.d. by mouth, and on this régime he had a normal bowel movement daily until his discharge 6 days later. Sent home on the drug he was seen 1 month later and seemed to the attending physician to be doing better than he had for years.

Case 2.—R. R., a boy of 12, was studied by Dr. G. H. Kagen at St. Christopher's Hospital. He had been constipated since birth having had no bowel movement without enemas or laxatives. The child was mentally retarded. Abdominal fecal masses could be palpated. Given B.M.C.U. in ascending doses beginning at 2 mg. t.i.d., his bowels soon began to move regularly. Whenever they failed to move the dose was raised, the highest attained being 2 mg. 6 times a day. Under this régime he had a daily stool for 3 weeks. Then, on December 30, 1939, the drug was omitted and his bowel action became most irregular, the child often going 4 days without a stool which was then usually secured by enema. On January 16, 1940, the drug was resumed in doses of 10 mg. daily. Movements were infrequent until January 24 when the first adequate evacuation occurred. Thereafter he had a good movement every 2nd or 3rd day until February 8th when the drug was omitted without the patient's knowledge, an inert tablet being substituted. He had no stool during the following week.

Paroxysmal Tachycardia. The slight action of B.M.C.U. on the circulation gave us reason to expect that it would be far inferior to mecholyl in arresting attacks of paroxysmal tachycardia and we have not used it for this purpose. Nevertheless, it seemed possible that it might prevent such attacks and for this purpose its long continued action would make it superior to mecholyl.

The ordinary case of paroxysmal tachycardia has attacks so infrequently and at such irregular intervals that the effectiveness of a drug designed to prevent them is very difficult to judge. At length we found a case having attacks so frequently that a study became possible.

Case 3.—A. F., an intelligent white man of 53, kept a careful record of his attacks in a notebook. Beginning in childhood, for the past few months he had had attacks once or twice a day. Many of these he could arrest himself by bending forward, the others usually stopped spontaneously within 2 to 4 hours. Ekg. showed typical auricular tachycardia. Otherwise his health was excellent.

After 5 days in the hospital as control period, the patient was given B.M.C.U. in ascending doses from 4 mg. to 8 mg. t.i.d. by mouth, receiving the largest dosage, 24 mg. daily, for a week. He noticed no side effects of the drug but the number of his attacks was unchanged. The patient believed that he was better able to arrest the attacks while he was taking the drug, but we had seen him stop several with great ease when not under its influence and so we were left in doubt whether the effect was a real one. Quinidine sulphate in doses of 0.2 gm. b.i.d. likewise had no influence in preventing attacks in this case.

Therefore we have obtained no evidence that choline derivatives are of value in preventing attacks of paroxysmal tachycardia although the action of mecholyl in arresting such attacks is well established.[17a,b]

Peripheral Vascular Disease. We have encountered 1 case of Buerger's disease in which severe rest pain was completely relieved by injections of either 0.4 mg. doryl or 4.0 mg. B.M.C.U. The patient was unable to distinguish between the two drugs but injections of inert solutions were identified immediately.

Spectacular relief of this type of pain by choline derivatives has occurred only rarely in our experience,[17a,c] but in a few patients this action has been very striking, the relief exceeding that secured by opiates. Slighter degrees of relief have occurred more frequently but in a majority of cases little, if any, relief can be secured by vasodilator drugs. Doryl and B.M.C.U. were identical in their effects on peripheral vascular disease in our experience.

A very interesting result, perhaps an effect on cerebral vessels, was secured in a case who also had peripheral vascular disease.

Case 4. A man of 65, with a long story of bouts of manic-depressive psychosis, had had a transient left hemiplegia 6 years before and intermittent claudication of the right thigh for 2½ years. Recently he had been subject to attacks of pallor and cold in the right leg. No pulses were palpable in either leg and there was atrophy of the right calf muscles. There was marked sclerosis of all palpable arteries and a positive Babinski on the left, but the physical examination was otherwise negative and the routine laboratory tests were normal. B. P. 125/80.

The day before admission he had been seized by attacks of transient numbness and weakness involving the left arm and left side of his face, with drooling from the left corner of his mouth. During these attacks the reflexes were normal, the parts involved flaccid. The attacks lasted about ½ hour and between them recovery was complete.

The patient had had 14 of these attacks in the 24 hours preceding admission. Under the belief that they were due to spasms of cerebral vessels analogous to those occasionally seen in his right leg, he was given 6 mg. B.M.C.U. subcutaneously and then 4 mg. t.i.d. by mouth. After the first dose the attacks stopped abruptly, he had only 3 mild ones, numbness without weakness, during the next 7 days and no serious attacks after that. He underwent slow mental deterioration and died, apparently of manical exhaustion about 3 months later.

Hypertension. Six out-patients suffering from essential hypertension of many years' duration were given B.M.C.U. by mouth, under the direction of Drs. H. A. Schroeder and Wm. A. Jeffers. Increasing amounts, ranging from 2 to 6, 10, and 12 mg. daily were given in divided doses over periods the shortest of which was 3 weeks, the longest 10 weeks. Placebo tablets of the same size and shape were given in control periods. The average blood pressure of these cases showed no significant change when they were taking the drug.

One patient had a diarrhea when taking 12 mg. daily but tolerated 10 mg. easily. There were no other untoward effects and this is the chief interest in the series.

Untoward Effects and Their Relief by Atropine. Our clinical results are what might be expected from the pharmacology of this drug. Our experience with untoward effects can be illustrated by

the experiments on normal volunteers in which the dose was deliberately raised to provoke them.

CASE 5. A medical student, A. W., age 23, weight 136, had been occasionally subject to asthmatic attacks. Given 10 mg. B.M.C.U. subcutaneously, the characteristic action began in about 3 min.; 5 min. after the drug he was slightly nauseated and 5 min. later he had abdominal cramps. Fifteen minutes after the drug he had a mild asthmatic attack. Atropine sulphate (0.6 mg. (gr. $\frac{1}{100}$)) was given subcutaneously and the site of the injection massaged vigorously. The asthma was relieved within 3 minutes but mild sweating, salivation, and cramps persisted and muscular tremors, accompanying a sensation of cold, appeared. The atropine was repeated 15 min. after the first dose and relief was complete within 10 minutes. Changes of blood pressure and pulse rate were negligible during this experience, except that after atropine the pulse rate diminished, as is regularly the case when that drug is used alone in small doses.

CASE 6. Another normal subject, H. P., age 23, weight 152 lbs., was given 8 mg. B.M.C.U. subcutaneously. The usual action appeared gradually but 30 min. after the administration of the drug abdominal cramps and pain in the bladder made him extremely uncomfortable. Atropine (0.6 mg. (gr. $\frac{1}{100}$)) was given subcutaneously and the discomfort disappeared in 15 min. However, about 3 hours later abdominal cramps and perspiration returned. A second dose of atropine then brought complete relief. Again there was no noteworthy effect on the circulation at any time.

Our experience with the untoward effects of B.M.C.U. may be summarized as follows. Like the other active choline derivatives used as medicaments, the drug produces asthma in patients subject to this disease. In other subjects, if the dose is raised until uncomfortable symptoms appear, abdominal cramps and painful spasms of the urinary tract appear first, at a time when changes in the circulation are usually negligible, and sweating and salivation only slight.

Subcutaneous doses of 10 mg. usually produced acute discomfort in medical students but many older patients could take this dose without any discomfort at all. Age seems to be a factor in the dosage of B.M.C.U. as it is with mecholyl.

Untoward effects can be relieved by atropine but a dose of 0.6 mg. (gr. $\frac{1}{100}$) given subcutaneously often proves too small. We now use 1.2 mg. (gr. $\frac{1}{50}$) subcutaneously and massage the site of the injection. Relief follows in a few minutes. Occasionally the choline action, outlasting that of the atropine, has reappeared several hours later, requiring additional atropine.

Discussion. A promising field of usefulness of B.M.C.U. is in combating the retention of urine not caused by organic obstruction. By its use catheterization after operation has been reduced to $\frac{1}{3}$ of its former frequency, to the relief of both the patients and the staff. A very similar result can be secured by doryl and the literature on this point is summarized in Table 4. When our data are compared it will be seen that we were less successful than some, more successful than others who used doryl. The grand average is slightly in favor of doryl, but in our own rather brief experience the use of

doryl in postoperative retention was not quite as successful as the published data had led us to expect, so we do not believe that there is a significant difference between the effectiveness of the two drugs.

We regard B.M.C.U. as superior to doryl because of the lack of side effects. Only rarely have our patients experienced anything uncomfortable. It is true that the side effects after doryl are usually of minor importance, but sweating, nausea, faintness, and malaise, were fairly common after that drug, both in our experience and in that summarized in Table 4. Also, especially after oral administration, doryl was irregular in its action and uncomfortable symptoms, chiefly malaise and nausea, appeared in some persons after receiving less than ½ the dose easily tolerated by others.[17c] The action of B.M.C.U. has been much more reliable in our experience. In addition, certain untoward effects of doryl could not be relieved by atropine,[17b] while uncomfortable symptoms after B.M.C.U. have yielded readily to atropine.

TABLE 4.—DORYL IN URINARY RETENTION, POSTOPERATIVE AND POSTPARTUM.

Author.	Type of case.	Subcutaneous dose, mg.	Success.	Partial success	Failure.
Schulze[13]	Postop.	0.25	80	..	28
	Postpart.	repeated if necessary	133	..	15
Moir[8]	Postop.	0.25	10	4	4
	Postpart.	0.25	4	4	12
Maxwell[7]	Postop.	0.25 repeated twice if necessary	15	..	2
Nolting and Altehabe[11]	Postop.	0.25	19	..	5
	Postpart.	0.25	39	..	4
Officer and Stewart[12]	Postop.	0.25	38	5	12
Brimberg[1]	Postop.	0.25 repeated if necessary	16	2	2
Schwartz[14]	Postop.	0.25	8	..	12
Kreutzman[7]	Postpart.	0.25	25	..	2
	Postop.	repeated once if necessary	25	..	3
Brown[2]	Postop.	0.25	25	..	5
Totals	Postop.	..	236 (74%)	11	73
	Postpart.	..	201 (85%)	4	33

Therefore, although the difference between the action of doryl and B.M.C.U., when given in clinically equivalent doses, is usually not striking, a prolonged experience indicates that the theoretical advantage of B.M.C.U. over doryl, its lack of nicotine-like action, is a practical advantage as well.

The knowledge that atropine completely obliterates all the effects of B.M.C.U. has given us confidence to explore the higher ranges of dosage as we would not have dared to do with doryl. Recent experience indicates that some patients tolerate large doses

extremely well, had we known this earlier our percentage of success would have been higher.

In the treatment of distention B.M.C.U. is often successful but we make no claim that it is more successful than other well known procedures. Its advantage lies in the fact that its action, if untoward, can be abolished at will. B.M.C.U. has also been used successfully in 2 cases of extreme constipation in children.

In peripheral vascular disease the effects of B.M.C.U. seem much like those of doryl; in an occasional case it causes striking relief of rest pain but the patients thus relieved are only a small fraction of the total number of these cases.[17c]

We have no evidence that the drug is of value in either hypertension or paroxysmal tachycardia.

In recent weeks our technique for the treatment of functional urinary retention has been as follows. As soon as the diagnosis is made we start B.M.C.U. giving 2 mg. t.i.d. by mouth and this is continued until voluntary or automatic voiding begins and then slowly withdrawn. In addition, if the bladder becomes over-distended we provide a bedpan and then give 2 mg. B.M.C.U. subcutaneously. If there is no voiding in half an hour we repeat this dose. If still unsuccessful within the next half hour, especially if pain is produced without voiding, we usually catheterize. But if the bladder becomes over-distended again we give 4 mg. subcutaneously repeating the dose in one-half hour if necessary before catheterizing. If there are no disagreeable side effects we continue to raise the dose in this manner until success is attained; in 1 case 10 mg. was required.

Any dose which empties the bladder once may be expected to have the same effect if retention occurs again. Therefore the successful dose is used until voluntary or automatic emptying is established.

The provision of a pan before administering the drug is an important detail of the technique, since the desire to void comes on quite rapidly in some persons; it can be resisted, and it may pass off if preparations are delayed.

Summary. 1. Beta methylcholine urethane, a stable choline derivative synthesized by Major at the suggestion of Simonart, has been studied in the clinic.

2. Having the typical choline action, this drug produces effects analogous to stimulation of parasympathetic nerves. These effects can be abolished by atropine. It is more stable than mecholyl and largely lacks the undesired nicotine-like action of doryl. It is probably for this reason that uncomfortable side effects are at a minimum. We regard it as superior to doryl for use in the clinic.

3. Given to 25 normal young adults, in suitable dosage, the drug caused increased peristalsis and a desire to void when its action on the heart and circulation, on salivation, and on sweating, was minimal.

4. The drug caused emptying of the bladder in 68% of 122 patients with postoperative urinary retention, reducing the necessity for catheterization by two-thirds.

5. It has also been used with benefit in patients with neurogenic bladders and in certain cases of abdominal distention, extreme constipation, and peripheral vascular disease.

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ALLERGIC INTESTINAL BLEEDING IN THE NEWBORN; A CLINICAL SYNDROME.

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While the occurrence of intestinal hemorrhage in children with gastro-intestinal disturbances due to allergy has long been recognized, this important manifestation of allergy in the newborn period seems to have escaped description in the pediatric literature. In the past 3 years, 6 such patients have been seen. The histories of these cases, which differ from each other only in very minor details, are so dramatically identical, as to form a definite clinical syndrome. The following cases are typical:

Case 1.—G. G., with a family history of allergy, was of normal birth, and weighed 9½ pounds at 1 month of age. Evaporated cow's milk feeding was begun at birth. For the first 3 weeks of life there was considerable "colic," during which period the nurse in charge was constantly demanding an increase of food, for the child seemed always hungry. Vomiting did not occur. At the age of 3 weeks, the stools, which until then had been normal, increased in frequency, became soft, and contained considerable flecking of bright red blood. The amount of blood in the stools increased until the entire stool mass, normal in form, was peppered throughout with millet-

seed sized specks of blood, and contained much mucus. The "colic" was exaggerated. Fever was not present.

After eliminating other possible causes of abnormal bleeding (melena), the diagnosis of allergic bleeding was considered. The child was then taken off cow's milk and put on human breast milk feedings. Within 48 hours after changing the feeding, the bleeding from the bowel ceased and the "colic" disappeared. The baby now seemed satisfied and the excessive hunger was no longer present.

One week later the feeding was again changed to cow's milk and there was a prompt return of the bloody stools within 24 hours. The cow's milk was then discontinued and breast milk started again, with prompt clearing of the blood from the stools a second time. After 3 months of breast milk feeding, goat's milk was substituted and was well tolerated. Solid foods were added to the diet at the usual time. At 1 year of age this child developed another allergic manifestation, typical diathetic eczema.

Summary. This baby, born of an allergic family, gained weight well and seemed in good health despite the early development of intestinal "colic." This latter symptom and excessive hunger were the only complaints until melena appeared. There was a prompt disappearance of symptoms on change from cow's to human breast milk. Goat's milk was later well tolerated. The child subsequently developed eczema.

CASE 2.—R. C., with a strong maternal family history of allergy, was born normally at term, weighing 7 pounds. He was immediately placed on feedings of evaporated cow's milk, on which he gained rapidly during the first 4 weeks of life. However, he seemed always hungry. "Colic," which developed at about 1 month of age, was partially relieved with sedatives. Even though large gastric peristaltic waves (indicative of pylorospasm) were visible on examination, vomiting did not occur. About 3 days after the onset of "colic," the stools became more frequent in number (5 to 6 daily) contained mucus, and were flecked throughout with small pinhead-sized blood specks. The blood was bright red. On 2 or 3 occasions the blood was free of fecal matter (about 1 or 2 drams in quantity). Fever was not present.

Within 48 hours after changing the feedings from cow's to goat's milk all of the intestinal symptoms disappeared and the stools became normal in character. At 5 months of age this child developed severe diathetic eczema.

Summary. This baby did well for the first 4 weeks on cow's milk feedings. He then developed pylorospasm with "colic." (It is interesting that vomiting did not occur even though large gastric peristaltic waves were present.) Prompt relief of symptoms resulted within 24 hours after removing cow's milk from the diet. This boy subsequently developed diathetic eczema.

CASE 3.—M. S. R., with a strong bilateral family history of allergy, was born normally at term. The birth weight was 5 pounds, 10 ounces. The weight at 5 weeks was 8 pounds, five ounces. Evaporated cow's milk feedings were begun at birth. Because of a tendency to loose and mucus-containing stools, many changes in the formula were tried, cow's milk always being used. The "colic," which did not appear until the third week of life, became suddenly worse 2 days prior to his hospital admission at the age of 5 weeks. On the first of these latter 2 days, the baby passed 6 bloody stools.

During the next 24 hours the amount of blood passed on several occasions was sufficient to wet a large part of each diaper. Bright red in color, the blood was passed with the stools, but seemed not admixed with them. An enema given on admission to the hospital returned bloody. (The cells on microscopic examination appeared fresh.) Due to the blood loss, a moderately severe anemia had developed. Because of the severe intestinal hemorrhage, the diagnosis of bleeding from a Meckel's diverticulum had been previously made and surgical intervention considered. Vomiting did not occur and fever was not present.

After clinical and laboratory studies, other causes for melena could be eliminated. Since bleeding from a Meckel's diverticulum is very rare at this early age, and because this case so closely resembled the others with milk allergy, the baby was taken off cow's milk and put on human breast milk feedings as a trial. Within 24 hours after this change in feeding, no fresh blood was found in the stools. After 48 hours the blood had completely disappeared, the stools were normal, and the "colic" had ceased, not to return again. Five days later the formula was changed to goat's milk. The baby has now been on goat's milk for 12 months without any return of the original symptoms.

Summary. This baby gained weight and seemed in good physical condition despite the early development of "colic" and of loose stools containing mucus. The bleeding from the bowel was so great as to produce anemia and suggest bleeding from a Meckel's diverticulum. (Two gastro-intestinal Roentgen ray studies were negative.) There was a prompt disappearance of all symptoms upon removing cow's milk from the diet.

CASE 4.—F. W. S., with a strong bilateral family history of allergy, was born by Caesarean section weighing 7 pounds, 7 ounces. Evaporated cow's milk feedings were begun at birth. This baby gained weight normally and seemed well until 5 weeks of age. At this time frequent vomiting and the passage of 5 to 6 loose, bloody stools daily began and continued until admission to the hospital at 7 weeks of age. The child had considerable "colic" and expelled much flatus. The blood in the stools was bright red and well mixed with the fecal matter. The stools contained considerable mucus.

From a period soon after birth this baby had peculiar "choking" attacks during which he became cyanotic and occasionally seemed in shock. These attacks over a period of subsequent months, have become less frequent and now appear as typical asthmatic attacks.

On examination at the age of 7 weeks, the baby was found to have a moderately severe anemia. Large gastric peristaltic waves were visible (pylorospasm). Roentgenograms of the lungs showed what may have been aspiration (lipoid) pneumonia. (We have seen similar lung changes in patients with pyloric stenosis.) On one occasion the mucus from the stool contained many eosinophils. Fever was not present.

After excluding other causes of melena, a diagnosis of allergic bleeding was made, and the formula changed from cow's milk to evaporated goat's milk. Within 48 hours of this change, the blood and mucus disappeared from the stools, and the vomiting and "colic" ceased. Following this, the gastric peristaltic waves were no longer observed.

After about 3 weeks on the goat's milk the intestinal symptoms reappeared, the stools becoming frequent and containing blood and mucus. With elimination of milk from the diet and the change of the formula to a soy-bean mixture, the intestinal symptoms permanently disappeared.

This child at the age of 4 months developed diathetic eczema.

Summary. This baby had peculiar "choking" spells which developed soon after birth, and now has what appears to be typical asthma. Beginning at the age of 5 weeks, this child developed frequent, loose, bloody stools containing mucus, with evidence of pylorospasm and "colic." The intestinal symptoms disappeared on removing cow's milk from the diet and changing the feedings to goat's milk. This baby proved later to be sensitive also to goat's milk, as the symptoms returned after 3 weeks on this food, to disappear permanently when a soy-bean feeding was substituted. Eczema has subsequently developed in this patient.

The summaries of each of these cases show a striking similarity. There was in each instance a strong family history of allergy, usually bilateral. In all of them cow's milk feeding was started immediately or within a few days after birth. Hunger, or what was thought by the mother to be hunger, was a constant complaint. In retrospect, this "hunger" probably represented abdominal discomfort, which was manifested as "colic." However, despite this abdominal distress, weight gain was not impeded; in fact, it was above average. The "colic" first appeared about 3 weeks after the onset of cow's milk feeding, and became progressively worse. Within a few days after the onset of the abdominal symptoms, loose stools appeared, soon to contain mucus and bright red blood. The amounts of blood varied from small pinhead-sized clots well admixed with the slimy stool, to profuse hemorrhage containing no fecal matter whatsoever. In each case there was prompt and complete disappearance of the blood from the stools within 48 hours after the withdrawal of cow's milk from the diet. The mucus in the stools and the "colic" disappeared shortly afterwards.

It is interesting that in 2 of the children, the "colicky" pains were associated with visible, large, gastric peristaltic waves, indicative of pylorospasm. This was probably a part of the generalized gastrointestinal spasm which disappeared when the other symptoms were relieved.

All the infants except one have developed diathetic eczema within a few months after the onset of the intestinal symptoms. One child developed asthma.

In none of the cases was bleeding from any other part of the body observed. In each case the bleeding and clotting times were normal. In no case did bleeding from the intestinal tract recur after the cows' milk was withdrawn, except in Case 4, where the baby seemed also sensitive to goat's milk, and where the melena disappeared when goat's milk was withdrawn and the child placed on a soy-bean mixture.

Intracutaneous tests with milk protein performed on the infants were negative. Passive transfer tests were not performed; it would seem useless to make them for cow's milk sensitization in these very young babies, for Lippard[1] found in a group of 28 eczematous infants,

given cow's milk over a period averaging 5 months, that only 1 of these babies had a positive passive transfer test for milk, even though 22 of them had developed antibodies against cow's milk (demonstrated by a positive complement fixation test for this milk).

Fever was not an accompanying symptom.

Discussion. These cases of gastro-intestinal allergy were all identical in that they were each cow's milk sensitive, having an onset of intestinal hemorrhage about 3 to 5 weeks after the starting of the cow's milk feeding, and a disappearance of the melena within 48 hours after the withdrawal of the cow's milk from the diet. In all except 1 case, goat's milk was well tolerated.

This interval of 3 to 5 weeks between the taking of cow's milk and the onset of severe gastro-intestinal symptoms, chiefly melena, is explainable by the observation of Lippard, Schloss, and Johnson,[2] who demonstrated that such a period of time was necessary for the maximal development of anti-cow's milk antibodies by the infant ingesting cow's milk. In other words, gastro-intestinal symptoms come on when the child is sufficiently sensitized (actively) to the cow's milk.

From the very rapid disappearance of symptoms, in every instance within 48 hours after the removal of cow's milk, one might assume that the intestinal spasm and hemorrhage were a local (intestinal wall) reaction. The mechanism of the local reaction is probably explainable by the following theory: First, the intestinal tissues are actively sensitized by the earlier ingestion of cow's milk or possibly through intra-uterine sensitization; and second, the severe intestinal reaction occurring subsequently, results from the presence of antigen (cow's milk) locally in the intestinal lumen, acting on the previously sensitized tissue. (This local reaction is similar to that seen in the positive skin test reactions or in contact dermatitis.) If this theoretical consideration were not valid and if the local effect were not the true mechanism, it would be difficult to explain the prompt disappearance of symptoms on withdrawal of the cow's milk from the diet. Lippard, Schloss, and Johnson[2] and Lippard[1] have shown that antibodies remain in the circulation of allergic (eczematous) babies for some time (months); in addition, the antigen (cow's milk) which is absorbed and present in the blood could hardly disappear so rapidly with the cessation of cow's milk feedings. Thus, if the intestinal phenomena were simply a local manifestation (shock organ) of a generalized reaction, the improvement after cow's milk withdrawal should be slow.

Since most of the babies could tolerate and remained well on the goat's milk feeding, it seems likely that sensitization in these cases was due chiefly to the lactalbumin fraction. If human breast milk is available, it is, of course, the preferable substitute, for the child may be also sensitive to goat's milk, as was found in one of the above cases.

It is not surprising that these infants, exhibiting such violent allergic manifestations in the newborn period, would develop other evidences of allergy at an early age (eczema). For this reason great care should be exercised when new foods are added to the infant's diet. A sufficient time interval between each new food addition should be allowed to observe whether or not allergic symptoms will develop.

It cannot be too strongly emphasized that even though there is considerable evidence to suggest an allergic etiology for the melena of a small infant, all of the more serious causes for intestinal hemorrhage should be thoroughly excluded before a final diagnosis of allergic melena is made. However, while this differential diagnosis is being investigated, one might safely remove the cow's milk temporarily from the diet and place the child on goat's milk feedings.

Even though the cases presented here are clearly cow's milk sensitive, there is no reason to believe that other foods given during this age period might not produce a similar clinical picture.

Summary. A well-defined clinical syndrome, in which the occurrence of intestinal bleeding is a prominent feature, is described in infants between 3 and 5 weeks of age who have developed an allergic sensitivity to cow's milk. "Colic" is also a constant symptom. These intestinal disturbances disappeared within 48 hours after the removal of cow's milk from the diet. In all except 1 case goat's milk was well tolerated.

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THE INCIDENCE OF ASPIRIN HYPERSENSITIVITY.

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In 1937 Prickman and Buchstein[7] stated that aspirin hypersensitivity is the most common form of drug allergy, and that it is to be looked for in individuals with a family history of allergy, and especially in asthmatics with nasal polyps. They reviewed the literature,* summarized a series of 33 cases of hypersensitivity to aspirin found there, collected 62 cases of their own and emphasized the dramatic consequences that may follow the ingestion of the drug by sensitive individuals. Four fatal cases have been reported.[4–6,9]

* For complete bibliography to 1937, see Prickman and Buchstein's article.

They were all asthmatic individuals. Three had given a previous history of severe reactions to aspirin. In 2 cases nasal polyps had been demonstrated. It is generally conceded that aspirin in certain instances may be a very dangerous ingestant, but proof seems to be lacking that aspirin hypersensitivity is as common as might be inferred from such reports. It is the purpose of the present study to assemble additional evidence concerning the incidence of aspirin hypersensitivity and to evaluate further its danger to allergic individuals.

The histories of 467 private and clinic patients were reviewed to determine if possible the incidence of aspirin sensitization among them. More than half of our patients were asthmatics. All of them were regarded as having some sort of allergy. Each was asked when his history was obtained: "Do you take aspirin?" and "What effect have you noticed from it?" The answers were recorded on the history sheet of each patient.

In 5 of these 467 cases aspirin or salicylates may have influenced the development of allergic symptoms. A patient with angioneurotic edema involving the lips, cheeks, and eyelids thought the taking of Stanback* precipitated her attacks. Another patient thought Stanback might cause her to develop an attack of asthma. A patient with angioneurotic edema thought her attacks were induced by aspirin or by B. C. Powders.* A patient with asthma complained of nausea after taking aspirin. Another reported that wheezing sometimes followed the use of salicylates. In no instance have we encountered the dramatic consequences occasionally described in the literature.

As has been pointed out by Cooke[2] differentiation must be made between drug idiosyncrasy and drug allergy. Drug idiosyncrasy is simply a normal pharmacologic response carried to an unusual degree. Drug allergy is an entirely different phenomenon which is sometimes produced by unbelievably minute quantities of the offending chemical.

Many persons complain of gastric discomfort, some of tachycardia, and others of mental exhilaration after takin aspirin. Nausea, vomiting, diarrhea, ringing in the ears and mental excitement are also recognized as early signs of aspirin overdosage, and in the susceptible even small doses may produce disagreeable symptoms. These disagreeable symptoms are irritative and toxic effects and not manifestations of allergy.

A group of 50 allergic patients were selected for detailed questioning. It was sought to determine whether they had experienced any of the above symptoms after taking aspirin and what had been their experience in taking quinine. Of the 50 persons questioned in detail, 44 suffered from asthma; 3 had atopic dermatitis; 1, urticaria; 1, vasomotor rhinitis; and 1, hay fever. All but 3 admitted taking

* Contains aspirin, acetanilide, potassium bromide and caffein.

aspirin, or a compound containing it; some took it as frequently as two or three times a week; some took it only once a year. Only 4 had experienced unpleasant symptoms which they thought referable to it. Two had rapid pulse and flushing, 1 had a depressed feeling and 1 complained of wakefulness. Of its effects on the allergic disorder itself, 33 stated they had never taken it for this purpose, 5 that it had had no effect, while 12 thought it had been beneficial. In none were allergic symptoms provoked. We found that 17 had never knowingly taken quinine. Those who had used it had done so only occasionally. Skin rashes had followed its use in 2 cases and in 1 instance dizziness resulted. No allergic symptoms were provoked.

To throw further light on the question of the frequency of the aspirin hypersensitivity in allergic patients, we undertook to give 5 grains of aspirin by mouth to each of 103 consecutive admissions to the Immunology Clinic, after a negative history of such sensitivity was secured. Each patient was observed at the end of 10, 30, 60 and 120 minutes, and note was made as to whether or not the allergic symptoms of which he initially complained were aggravated or improved. In this group there were fourteen who maintained that "the medicine" had made them feel better. Two asthmatics stated that they had a slight sense of constriction in the chest. In both instances the symptoms were transitory and may not have been the result of the drug. None of these 103 patients reacted violently to aspirin.

Patch tests with aspirin in our experience have been uniformly negative. We have not attempted scratch or intracutaneous tests in this type of sensitivity.

We have many times encountered non-allergic patients who said they could not take aspirin, but who could usually be given it without any discomfiture if it were disguised in a capsule.

The opinion of a group of 95 allergists of this country concerning the frequency of aspirin and quinine sensitivity was sought. We had 46 answers to the questions: "How many cases of aspirin sensitivity have you encountered and what percent does this represent of all the allergic patients you have seen?" and "How many cases of quinine sensitivity have you encountered and what percent does this represent of all the allergic patients you have seen?" A number of correspondents gave figures that were admittedly approximations, but when everything is considered this did not negative the value of the experience of so large a group. Omitting those answers which were too indefinite to use, and one or two estimates which were out of line with the average experience of the group, we calculated that the total number of allergic patients seen by the 22 physicians whose answers could be used, was approximately 90,000. Among this large number of patients, approximately 170 had shown evidence of aspirin sensitivity. This represents 2 in 1000 (0.2%).

Among the same group of patients 71 instances of quinine sensitivity were reported.*

ASPIRIN AND QUININE SENSITIVITY. OPINION OF FORTY-SIX ALLERGISTS TABULATED.

	Location.	Number seen. A.	Number seen. Q.	Per cent. A.	Per cent. Q.	Total patients.	Remarks.
1.	Alabama	1	3	0.2	0.6	500	
2.	Louisiana	2	1	0.25	0.12	800	
3.	New York	12*	1*	0.1	0.01	10,000	
4.	Illinois	10*	10*	0.2	0.2	5,000	
5.	Colorado	0	3	0	0.03	10,000	
6.	Michigan	4*	2*	0.1	0.05	4,000(?)	
7.	Ohio	3	2	0.6	0.4	500	
8.	Virginia	9	0	3.6	..	250	
9.	Missouri	5	3	0.1	0.05	5,000	
10.	Louisiana	5	0	0.5	..	1,000	
11.	Missouri	10	5	0.5	0.25	2,000	
12.	Ohio	14	2	0.1	0.01	14,000	
13.	Illinois	4	6	1.0	1.5	400	
14.	Ohio	20	7	0.4	0.15	5,000	
15.	New Jersey	15	5	0.5	0.15	3,000	
16.	New York	2	2	0.4	0.4	500	
17.	Virginia	2	6	0.5	1.5	400	
18.	Washington	4–5	2–3	1.0	0.5	500	
19.	Pennsylvania	1	0	0.1	0	1,000	
20.	Pennsylvania	15	3	0.1	0.02	15,000	
21.	Virginia	120*	120*	2.0	2.0	6,000	
22.	Michigan	4	5	0.2	0.25	2,000	
23.	Wisconsin	27	0	0.5	0	5,400	
24.	Minnesota	117	6				
25.	Nebraska	5	2	..	..	..	Very small per cent
26.	Texas	10*	15–20				
27.	New York	2	1+				
28.	Pennsylvania	6	1				
29.	Illinois	3	0				
30.	Alabama	2	1	1.0(−)	1.0(−)		
31.	New York	1	1	..	..	..	In several thousand cases
32.	California	15	Few	..	..	..	Very small per cent
33.	Arizona	25*	?	..	..	..	Fraction of 1 per cent
34.	New York	6–12	3	1.0(−)	1.0(−)		
35.	Alabama	Few	Numerous	..	..	..	Aspirin rare, quinine frequent
36.	Texas	Few	Few				
37.	Massachusetts	..	..	0.25*			
38.	Tennessee						
39.	Georgia	..	..	5.0	1.0	..	5 times as many aspirin as quinine
40.	Minnesota	0	0				
41.	New York	Common	Common				
42.	Pennsylvania	?	?				
43.	Missouri	Few	Few	..	..	..	Very small per cent
44.	Arizona	Many	Rare	25.0	?		
45.	Illinois	Many	1				
46.	Minnesota	117*	6				

A., Aspirin. Q., Quinine.
* From same clinic as 24.

We next undertook to discover the annual consumption of aspirin and quinine in this country. We found that in 1937 there was sold in the United States alone 5,143,672 pounds of aspirin.[3] This represents a consumption of one-half an ounce (240 gm.) or 48 tablets on the average by each person in the United States annually. In the same year 3,458,009 ounces of quinine were consumed in this country.[8] The American people, therefore, consume about seventeen times as much aspirin a year as quinine. If, out of a group of 90,000 allergic individuals, 170 were aspirin sensitive, and 71 quinine sensitive, with only one-seventeenth as much quinine being consumed as aspirin, it would seem that the chance of a given

* Reactions to arsphenamine occur once in 126 cases.

individual's being sensitive to quinine is at least seven times as great as the chance of his being sensitive to aspirin. These figures suggest another interpretation of the statement of Coca *et al.*[1] and of Prickman and Buchstein[7] that aspirin ranks first among allergy producing chemicals.

Conclusions. The increasing use of synthetic drugs of greater and greater structural complexity is undoubtedly making drug allergy one of the most important subdivisions of the field of allergy. Aspirin is a synthetic drug and is consumed in enormous quantities. It is capable of producing dangerous, even fatal reactions in sensitive individuals. Considering the number of persons who annually take aspirin, and employing quinine for a comparison, it is not thought to be, as has been claimed, the drug to which sensitization most easily develops. In fact, probably not more than 2 out of 1000 persons are sensitive to it, and of these a much smaller proportion react violently. This does not indicate the employment of less caution in the administration of aspirin to allergic persons, but it should give comfort to some, who, since the publication of Prickman and Buchstein's paper, have administered it with apprehension.

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MOTILITY AND CHEMOTAXIS OF LEUKOCYTES IN HEALTH AND DISEASE*

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AND

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The resistance of a patient to bacterial infection depends in part on the activity of his polymorphonuclear leukocytes. An important function of these cells is to react to bacteria in the tissues by moving toward them, a response known as chemotaxis. Through chemotaxis, leukocytes are brought into contact with bacteria, and opportunity is given for phagocytosis and subsequent intracellular digestion.

* This investigation was aided by a grant from the Committee on Therapeutic Research of the Council on Pharmacy and Chemistry of the American Medical Association.

The present paper is concerned with the question, Is the movement of leukocytes toward bacteria altered by disease? If leukocytes, during an illness, move more rapidly or more directly toward the microörganisms, a greater number of cells would reach the infected area in a given time, and the patient's resistance to infection should be increased. The opposite effect would be expected if leukocytes should move more slowly or less directly toward the bacteria. Consequently it seemed of interest to measure the rate and the direction of locomotion of leukocytes from acutely ill persons and from persons not acutely ill in order to find out whether significant differences exist.

Method. Two groups of patients were selected from the wards of the hospital.* In the first group were included patients who were acutely and seriously ill with such infections as pneumonia or typhoid fever, or who were suffering from acute cardiac decompensation (see Table 1). In the second group were included patients not acutely ill, most of them convalescing from chronic infections or in the hospital because of gout, malnutrition or nerve trauma (Table 2). All these patients, like those of the first group, were confined to bed.

In order to control such variable environmental factors as the time of day, the temperature of the room and the age of the bacterial culture, the observer's leukocytes (assumed to be normal) were always used as a standard with which the patient's leukocytes were compared.

A minute clump of bacteria from an agar slant was placed on a glass slide and allowed to dry, where it formed a flat, circular or oval object with a diameter of about 0.5 mm. A drop of blood obtained by puncturing the finger was placed on a coverslip and lowered on the clump of bacteria in such a way that the blood spread evenly between slide and coverslip. The preparation was sealed with petrolatum to prevent evaporation and observed with the high power of the microscope at 37° C.

By means of a drawing ocular, the image of a microscopical field containing part of the bacterial clump was projected on paper, and the position of each polymorphonuclear leukocyte in the field was recorded at intervals of 1 minute for 10 minutes, unless the cell came to rest within a shorter time. A record obtained in this way is shown in Chart I.

From such a record two values are obtained, first, the rate with which the leukocytes approached the bacteria, and, second, the rate of locomotion irrespective of direction. The rate of approach of a leukocyte to bacteria is found by measuring the dotted line AB, the shortest distance between A and the bacteria (63 mm. in the original record) and dividing by the number of minutes of observation (10). Corrected for magnification (1 mm. on the original record corresponds to 2.6 microns) the rate of approach for this cell is $63 \times 2.6 \div 10 = 16.4$ microns per minute. The rate of locomotion is found by measuring and adding all components of the line AC (72 mm. on the original record), dividing by the number of minutes and correcting for magnification. For the leukocyte in question the value is $72 \times 2.6 \div 10 = 18.7$ microns per minute. In this way average values were found for each record and for all the records of each patient. Details of the computation have been given in an earlier paper.[3]

Results. In most experiments the organism used to attract leukocytes was *Staph. aureus;* less often, pneumococcus or typhoid

* The authors are indebted to the Medical and Surgical Staffs of the Hospital of the University of Pennsylvania for affording them facilities for this investigation.

bacillus, the same bacteria being used with leukocytes of the observer as with those of the patient. *Staph. aureus* and pneumococcus were tested alternately with the cells of one patient (Case 1, Table 1) and no significant difference was found in the effect of these two organisms. From present evidence it appears that leukocytes from a patient with an acute infection react to the causative organism in the same way as to other bacteria.

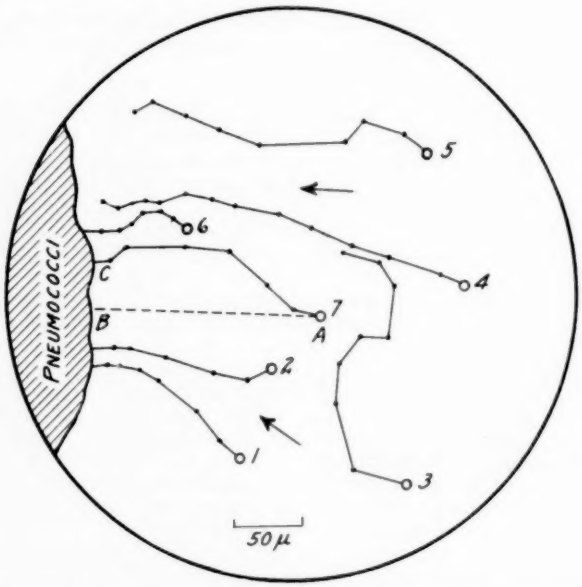

CHART I.—The reaction of polymorphonuclear leukocytes to pneumococci. Part of the clump of bacteria is shown to the left. The paths of 7 leukocytes were recorded for 10 minutes, or until the cells reached the bacteria. All the leukocytes moved toward the bacteria.

In Table 1 are given the results of experiments designed to answer the questions: Do polymorphonuclear leukocytes of acutely ill persons move toward bacteria more or less rapidly than do those of a normal person, and is there a difference in the rate of locomotion (irrespective of its direction)? Data bearing on the first question are found in the columns which give the average rate of approach of leukocyte to bacteria. Comparing values for each of the 12 patients with correspondng values for the observer, it is seen that in every instance the value for the patient was less than that for the observer, the averages for the series being respectively 9.7 and 16.1 microns per minute. That is, on the average the leukocytes of the ill person approached bacteria 40% less rapidly than did those of the observer.

The rates of locomotion, irrespective of direction, are compared

in the next columns. In each instance the patient's leukocytes moved more slowly than the observer's, the averages being respectively 14.9 and 21.1 microns per minute, a reduction of 29% in the speed of the patients' cells.

TABLE 1.—CHEMOTAXIS AND LOCOMOTION IN LEUKOCYTES OF ACUTELY ILL PATIENTS.

Case.	Diagnosis.	No. of experiments.	Bacteria used in experiments.	Rate of approach, microns per min.		Rate of locomotion, microns per min.		Chemotactic ratio.	
				Pt.	Ob.	Pt.	Ob.	Pt.	Ob.
1	Lobar pneumonia	6	Pneumococ. *Staph. aureus*	9.2	13.9	15.0	18.7	0.62	0.74
2	Lobar pneumonia	2	Pneumococ.	12.0	16.3	16.6	21.4	0.72	0.76
3	Lobar pneumonia	2	*Staph. aureus*	13.9	20.3	19.8	23.9	0.70	0.85
4	Lobar pneumonia	2	*Staph. aureus*	11.1	13.2	16.7	17.9	0.66	0.74
5	Bronchopneumonia	2	*Staph. aureus*	9.7	14.0	15.6	20.9	0.62	0.67
6	Lobar pneumonia	2	*Staph. aureus*	9.4	18.7	15.1	25.1	0.62	0.74
7	Rhinosinusitis	1	*Staph. aureus*	12.4	23.9	17.2	29.5	0.72	0.81
8	Influenza	2	*Staph. aureus* *E. typhosa*	6.0	8.4	10.0	12.0	0.60	0.70
9	Typhoid fever	4	*E. typhosa*	5.3	10.7	8.9	15.0	0.60	0.71
10	Therapeutic pyrexia Buerger's disease	2	*Staph. aureus*	10.7	14.3	16.6	19.4	0.64	0.74
11	Acute cardiac decompensation, rheumatic	2	*Staph. aureus*	9.9	12.9	15.9	17.1	0.62	0.75
12	Acute cardiac decompensation, luetic	1	*Staph. aureus*	7.1	26.2	11.5	31.6	0.62	0.83
	Mean	...	...	9.7	16.1	14.9	21.1	0.65	0.76

Pt., Patient. Ob., Observer.

The rate of approach of leukocytes to bacteria, their rate of locomotion and the ratio of these values (chemotactic ratio) are given for patients and for the observer. It is seen that values for patients' leukocytes were in every instance less than those for the observer.

In the last two columns are given the chemotactic ratios. These values are obtained by dividing the rate of approach by the rate of locomotion. The chemotactic ratio indicates how directly leukocytes travel toward bacteria, irrespective of the rate of movement. The ratio would be 1 if leukocyte moved straight toward bacteria, but is usually a fraction of 1 since the path is rarely perfectly direct.[2] In each instance this ratio is higher for the observer than for the corresponding patient.

Having thus found that leukocytes of acutely ill patients moved less rapidly and less directly toward bacteria than did the observer's, we now compared the observer's leukocytes with those of a series of patients not acutely ill. In these experiments a very different result was obtained (Table 2). It is seen that comparing column with column as described above for Table 1, there is no consistent difference between the leukocytes of the patients not acutely ill and those of the observer; the differences between the averages, as shown in the bottom row, are slight and not significant. We conclude therefore that leukocytes of the acutely ill persons moved less rapidly and less directly toward the bacteria than did those of the patients not acutely ill.

TABLE 2.—CHEMOTAXIS AND LOCOMOTION IN LEUKOCYTES OF PATIENTS NOT ACUTELY ILL.

Case.	Diagnosis.	Rate of approach, microns per min.		Rate of locomotion, microns per min.		Chemotactic ratio.	
		Pt.	Ob.	Pt.	Ob.	Pt.	Ob.
1	Pulm. tuberculosis	13.5	13.1	16.8	18.8	0.80	0.70
2	Infect. mononucleosis	16.6	15.6	19.5	20.4	.85	.76
3	Postop. adhesions	9.4	7.8	14.7	12.9	.64	.60
4	Bronchitis	20.4	15.2	25.1	17.2	.81	.88
5	Chr. brucellosis	13.8	16.0	16.7	19.1	.83	.83
6	Gout	13.9	15.2	21.6	21.4	.64	.71
7	Hypertrophic arthritis	19.6	21.4	24.4	24.5	.80	.88
8	Malnutrition	14.3	18.8	20.0	21.5	.71	.88
9	Chr. sinusitis	14.2	8.6	19.6	14.9	.73	.58
10	Nerve trauma	14.4	20.0	21.2	25.6	.68	.78
	Mean	15.0	15.2	20.0	19.6	.75	.77

There is no consistent or significant difference between values obtained with patient's leukocytes and those of the observer. The bacteria used were *Staph. aureus*. One experiment was made on each patient.

Using a statistical method, these conclusions were verified by comparing directly the data obtained from the two groups of patients.*

Another observation was made in these experiments. In several instances in which the preparations were reëxamined after 2 or 3 hours, great decrease in locomotion and in chemotactic response was observed in the acutely ill patient's leukocytes, whereas the observer's cells maintained their activity unimpaired. As an example is cited one of the experiments on Case 1, Table 1, a patient suffering from lobar pneumonia. When first examined, leukocytes from this patient were found to approach bacteria at the average rate of 11.0 microns per sec., and their average rate of locomotion irrespective of direction was 15.3 microns per sec. Two and a half hours later the values were respectively 4.5 and 10.3 microns per min. In contrast to the marked deterioration of these leukocytes, those of the observer during the same time declined in activity only slightly; when first examined, the rate of approach to bacteria was 14.4 microns per min., the rate of locomotion, 18.5 microns per min. Two and a half hours later, corresponding values were 11.9 and 17.3 microns per min.

Still greater functional deterioration of ill patients' leukocytes was found in other experiments. When preparations were reëxamined after 2 to 3 hours, locomotion had practically ceased. A similar difference in rate of deterioration between leukocytes of ill patients and those of normal persons was noted by Philipsborn.[4]

* The statistical method used was that recommended by Fisher[1] for dealing with small samples. Values for the rate of approach of patient's leukocytes in Tables 1 and 2 were compared. The probability that equal or greater differences between the means would occur through random sampling was found to be less than 1 in 100. The difference is therefore regarded as significant. The same probability (less than 1 in 100) was found on comparing rates of locomotion and also on comparing chemotactic ratios.

Discussion. It has been shown that leukocytes from a series of acutely ill persons moved less rapidly and less directly toward bacteria than did the cells in control series. Further observations have suggested that the leukocytes of acutely ill persons are relatively unable to tolerate the unfavorable conditions of experiments *in vitro*, and deteriorate more rapidly than normal cells.

In severe illness, not merely whole organs such as the heart and kidneys are depressed in function but individual cells such as leukocytes. This fact is emphasized in these experiments, which afford a quantitative measure of alteration in function of leukocytes in ill persons. The alterations in function thus established would tend to reduce the resistance of the patient to bacterial infections by lengthening the time required for mobilization of leukocytes.

Summary. The activity of polymorphonuclear leukocytes from a series of patients acutely ill, most of them with infections, was compared *in vitro* with that of the observer's leukocytes and of leukocytes from patients not acutely ill. Decreased rate of locomotion and less direct approach to bacteria were shown by leukocytes of the acutely ill persons. In leukocytes of some patients who were gravely ill decline in motility and chemotactic response was progressive whereas the observer's leukocytes maintained their activity unimpaired for hours. The functional changes observed would tend toward lowering resistance to infection. These experiments emphasize the fact that in severe illness the function not merely of whole organs but of individual cells is depressed, and they afford a method for quantitative measurement of changes in cellular function.

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BOOK REVIEWS AND NOTICES

ARTHRITIS AND ALLIED CONDITIONS. By BERNARD I. COMROE, A.B., M.D., F.A.C.P., Instructor in Medicine, University of Pennsylvania; Ward Physician, Hospital of the University of Pennsylvania. Pp. 752; 200 illustrations. Philadelphia: Lea & Febiger, 1940. Price, $8.50.

THIS volume is intended to "be of practical value" to the physician. It begins with an outline for the study of the rheumatic patient and ends with a scheme for the organization of an arthritic clinic. Included between is a detailed discussion of the disease conditions embraced in the rheumatic syndrome. Each chapter is documented with numerous references to the most important literature of recent years. Chief items, diagnostic, therapeutic, indications, and contraindications, are "boxed" for emphasis. This arrangement makes for ready reference. The etiologic classification follows that adopted by the American Rheumatism Association. Various therapeutic methods are critically evaluated, and the author indicates his choice of a well rounded régime in each instance. Many of the recent "fads" are mentioned to be condemned. The hazards of gold, large doses of vitamin D, and other measures are appropriately stressed. A noteworthy inclusion is the chapter on "Spas" with a list of those which deal primarily with arthritis and their cost to the patient. The illustrations are well chosen and numerous. The format is excellent and typographical errors few. Details of the Rourke-Ernsteine sedimentation test, which is widely used in this country, are omitted. Metric doses for drugs might have been profitably added. The discussion of fibrositis seems inadequate in view of its importance in the rheumatic syndrome.

The general practitioner will find in this book the answer to the puzzling problems which arise in treating arthritis. It should receive wholehearted acceptance by the medical public and is recommended unqualifiedly. M.B.

DYNAMICS OF INFLAMMATION. An Inquiry into the Mechanism of Infectious Processes. (Experimental Biology Monographs.) By VALY MENKIN, Department of Pathology, Harvard University Medical School. Pp. 244; 50 illustrations. New York: The Macmillan Company, 1940. Price, $4.50.

THE studies of Dr. Menkin have added much to our knowledge of inflammatory reactions. In this monograph he has ably summarized his own investigations as well as the extensive literature in this field. After an historical survey of the subject he discusses the part played by the capillaries, the migration of leukocytes, the cellular sequence, and the phagocytic theory. Next, follow chapters on inflammation in relation to immunity, on the localization of foreign materials in areas of inflammation, on allergic and anaphylactic inflammation, on the rôle of lymphatics, and on inflammation and bacterial invasiveness in relation to resistance. In a concluding chapter, the views expressed are briefly recapitulated. A well selected list of 417 references is appended.

Inflammation has long been regarded the "keystone to an understanding of pathology." The reading of this book is warmly recommended to investigators and even more to practitioners. B. L.

ÜBER DIE INTEGRATIVE NATUR DER NORMALEN HARNBILDUNG. Teils I, II and III. (Teil III. Systematischer Rückblick.) By GÖSTA EKEHORN, D:R. Med. Stockholm. Pp. Teils I and II, 1429; Teil III, 292. Helsingfors: Privately Published. Printed by Mercators Trycheri, 1938.

THESE volumes of over 1700 pages are an extension of the author's previous monograph "On the Principles of Renal Function," published in 1931. In the first two volumes are discussed in considerable detail the experimental studies upon which is based the present-day concept of the function of the kidney; the last volume summarizes these studies. The work affords a comprehensive survey over the entire field of renal physiology, and will no doubt serve as a valuable reference book for specialists.

B. L.

PATHOLOGICAL HISTOLOGY. By ROBERTSON F. OGILVIE, M.D., F.R.C.P. (Edin.), Lecturer in Pathology, University of Edinburgh; Senior Pathologist, Royal Infirmary, Edinburgh; Pathologist, Deaconess Hospital, Edinburgh; Examiner in Pathology for the Triple Qualification. Foreword by A. MURRAY DRENNAN, M.D., F.R.C.P. (Edin.), Professor of Pathology, University of Edinburgh. Pp. 332; 220 photomicrographs in color by T. C. DODDS, F.R.P.S., F.I.B.P., Senior Technician, Pathology Department, University of Edinburgh. Baltimore: The Williams & Wilkins Company, 1940. Price, $8.50.

THE purpose of this book, and the general description of its contents are so well stated by the author that we shall quote his words: "This volume is designed to act as a companion to a standard textbook of Pathology and to meet the need of the student in the class of morbid histology and of the graduate seeking more specialised knowledge in pathological processes.

"Its text is based on a series of lectures in pathological histology delivered at Edinburgh University and gives an account of the tissue-changes produced by those diseases most commonly encountered in Great Britain. Following a scheme adopted by many textbooks of Pathology the earlier chapters deal with the phenomena of degeneration, vascular disturbances, inflammation, repair and tumours, while the later chapters are devoted to special diseases of the systems. That its value might be enhanced each microscopical description is introduced by a macroscopical account of the diseased tissue or organ and, in particular instances, brief space is also given to the etiology of the condition and to the significance of the microscopical findings in relation to the nature of the disease.

"The feature of the book is the illustration of its text by 220 photomicrographs in colour."

These colored photographs are indeed very excellent, and should be much more helpful to the student than the usual black and white illustrations. The text is clear and well written. The Reviewer has no doubt that this work will prove a helpful companion to the more complete textbooks on pathology, and as such it is warmly recommended. B. L.

PHYSICAL THERAPY FOR NURSES. By RICHARD KOVÁCS, M.D., Clinical Professor and Director of Physical Therapy, New York Polyclinic Medical School and Hospital; Attending Physical Therapist, Manhattan State, Harlem Valley State and West Side Hospitals, etc. Second Edition, thoroughly revised. Pp. 335; 99 illustrations. Philadelphia: Lea & Febiger, 1940. Price, $3.25.

THE aim of the author in writing this book is to "present as concisely as possible the subject of physical therapy—exclusive of *X*-rays and Radium—in a manual that may be used in the curricula to enable the average nurse to assist the physician in administering treatments by physical means."

This text covers more than the essential material required by the average nurse and so provides somewhat more information than is usually given in lectures covering this subject. However, the book is simply written and is an excellent reference book for the library of all schools for nurses.

M. S.

ON OXIDATION, FERMENTATION, VITAMINS, HEALTH AND DISEASE. (The Abraham Flexner Lectures, Series No. 6.) By ALBERT V. SZENT-GYÖRGYI, M.D., PH.D. (Cantab.), D.H.C., Prix Nobel, Professor of Medicine and Organical Chemistry, University of Szeged. Pp. 109. Baltimore: The Williams & Wilkins Company for Vanderbilt University, 1939. Price, $2.00.

THE Flexner lectures of the Vanderbilt University Medical School are given biennially by an eminent scientist or physician within a period of two months during which he is associated with the teaching staff and the students of one department. The 1939 lectures by the Hungarian biochemist Albert von Szent-Györgyi cover the field of biological oxidations to which he has made many contributions, the best known of which is probably the isolation of an active reducing substance from the adrenal gland and from plant cells, which he later showed to be the antiscorbutic substance, vitamin C. The material is presented in a manner to inspire not only the medical students for whom it was originally intended, but anyone who enjoys a beautiful presentation of a scientific subject. E. W.

MANUAL OF PERIPHERAL VASCULAR DISORDERS. By DAVID W. KRAMER, M.D., F.A.C.P., Assistant Professor of Medicine, Jefferson Medical College; Assistant Physician and Chief Clinical Assistant, Vascular Clinic, Jefferson Hospital, etc. Pp. 448; 126 illustrations. Philadelphia: The Blakiston Company, 1940. Price, $6.00.

THIS manual of peripheral vascular disorders is a timely one when new advances in this field, both in diagnosis and treatment, have come so rapidly. The author has furnished a simple and straight-forward account of the various diagnostic procedures and clinical pictures of occlusive and vasomotor vascular disorders. He has outlined the accepted methods of treatment. The procedures of oscillometry, histamine test and vasodilatation test are well presented and the author calls attention to the difference between tests for the pressure of pulsating arteries and examinations to determine the state of peripheral blood flow. The book is essentially a practical manual with few references to fundamental physiology or chemistry. The significance of tissue metabolism in relation to blood flow is not discussed. The use of heparin in thrombus and embolism is mentioned only in the treatment of the rare condition of "Essential Thrombophilia." This manual should be useful for practitioners and students of medicine. The index is complete and a good bibliography is to be found at the end of each of the four parts of the book. N. F.

PRACTICAL BEDSIDE DIAGNOSIS AND TREATMENT. By HENRY JOACHIM, M.D., Chief-of-Medicine, Israel-Zion and Beth Moses Hospitals; Director of Medicine, Cumberland Hospital and Jewish Sanitarium and Hospital for Chronic Diseases, Brooklyn, etc. Pp. 828. Springfield, Ill.: Charles C Thomas, 1940. Price, $7.50.

ACCORDING to the publisher: "Most differential diagnoses stress signs and symptoms. This book stresses Diseases!" This innovation in the arrangement of a text of differential diagnosis is a welcome relief from the tabulation of symptoms and signs which almost invariably led the reader

of previous decades to a wrong diagnosis. Its arrangement and content are those of a text of medicine, subject to the advantages and disadvantages of reflecting one man's experience. There are errors inexcusable in even a first edition: *e. g.*, the Hines-Brown cold pressor test is attributed to Landis, p. 207. W. J.

BLOOD GROUPS AND BLOOD TRANSFUSION. By ALEXANDER S. WIENER, A.B., M.D., Serologist and Bacteriologist in the Office of the Chief Medical Examiner of New York City. Second Edition. Pp. 306; 52 illustrations. Baltimore: Charles C Thomas, 1939. Price, $5.00.

A COMPLETE and authoritative survey of an important and highly practical subject. This new edition has been brought up to date by the inclusion of much new material, as evidenced by 80 additional pages. Workers in the field will welcome this volume. R. K.

CANCER: A Manual for Practitioners. The Committee on Publication: GEORGE W. HOLMES, M.D., Chairman, ERNEST M. DALAND, M.D., SHIELDS WARREN, M.D., CHANNING C. SIMMONS, M.D., Editor. Pp. 284. Boston: Department of Public Health, 1940.

AN important phase of the cancer problem is the education of the practitioner in the principles of early diagnosis and in the methods of treatment which are recognized at the present time. It is almost impossible for the physician engaged in practice to keep up with the enormous current literature on malignant disease, and still more difficult for him to separate the wheat from the chaff in the reading which he is able to do. This Cancer Manual has been thoughtfully prepared in answer to this need by a committee representing the Massachusetts Medical Society and the American Society for the Control of Cancer. It contains brief articles on "Historical Trends in Cancer," "Present Trends in Cancer Research," and on general principles of diagnosis and treatment in malignant disease. The main body of the book is then devoted to consideration of malignant tumors of each anatomic region. Emphasis is placed throughout on the practical aspects of symptomatology, diagnosis, treatment, and prognosis of each type of tumor. The majority of the contributing authors are members of the faculty of the Harvard Medical School who have been active in promoting the campaign against cancer in the State of Massachusetts through the Hospitals and Clinics of the Department of Public Health and the Harvard Cancer Commission. The cancer manual which they have prepared reflects the splendid work which is being done by these organizations. The book is highly recommended to all physicians who wish to obtain a rapid review of the clinical aspects of cancer.

It is stated in the Preface that arrangements have been made to distribute this volume free to all practitioners of Massachusetts. It would be an important contribution to cancer education if a similar plan could be carried out in many other states. J. L.

EXPERIMENTAL INVESTIGATIONS IN SERUM ALLERGY WITH REFERENCE TO THE ETIOLOGY OF RHEUMATIC JOINT DISEASES. By EGON BRUUN, M.D. Pp. 229; 49 illustrations. Copenhagen: Einar Munksgaard; London: Oxford University Press, 1940. Price, Dan. Kr. 24.

A REVIEW of previous literature and presentation of the author's experimental evidence on the rôle of allergy in the production of the lesions of rheumatic fever and infectious osteoarthritis. By various modes of sensitizing rabbits with horse serum, the author produced joint lesions which he considers analogous to the lesions of human rheumatic diseases. He believes that his findings lend support to the view that allergy induced by

bacterial (probably streptococcal) action is the mechanism concerned in the production of rheumatic joint lesions in man. The monograph is the author's thesis for the Doctorate in Medicine at Copenhagen. R. K.

CHEMISTRY AND MEDICINE. Papers Presented at the Fiftieth Anniversary of the Foundation of the Medical School of the University of Minnesota. Edited by MAURICE B. VISSCHER, PH.D., M.D., Professor of Physiology at the University of Minnesota. Pp. 296; 73 figures and 18 tables. Minneapolis: The University of Minnesota Press, 1940. Price, $4.50.

AT the celebration, in October, 1939, of the fiftieth anniversary of the foundation of the Medical School of the University of Minnesota, it was decided, in the words of the Preface, to focus the scientific program upon the single theme: "Some Trends in Medical Progress, with Particular Reference to Chemistry in Medicine." The present volume contains the papers presented on this occasion by 14 speakers, representing in equal numbers the University of Minnesota and outside scientific institutions. The diverse and interesting program included papers in the fields of colloid chemistry of membranes (H. Freundlich), osmotic work in living systems (M. B. Visscher), concentration by the kidney (J. P. Peters), vitamin chemistry (L. I. Smith), the rôle of fats in the diet (G. O. Burr), heparin and thrombosis (C. H. Best), immunity (M. Heidelberger), animal viruses (R. G. Green), sulfanilamide (P. H. Long), urinary antisepsis (H. F. Helmholz), convulsive reactivity (I. McQuarrie), analysis of nervous action (H. S. Gasser), nervous regulation of visceral processes (D. W. Bronk), and the chemical mediation of nervous impulses (W. B. Cannon). The timely nature of these subjects, the authority of the authors in their respective fields, and the generally readable and scientific, but not unduly technical, character of the contributions should gain for the volume a wide circle of readers. M. J.

YOUR ALLERGY, AND WHAT TO DO ABOUT IT. By MILTON B. COHEN, M.D., Director of the Asthma, Hay Fever and Allergy Foundation, Cleveland, and JUNE B. COHEN. Pp. 177. Philadelphia: J. B. Lippincott Company, 1940. Price, $1.50.

A TREATISE on allergy, written for laymen, in a chatty readable style that only occasionally bogs down in scientific detail. There is ample justification for such a book: allergy depends upon an inherited characteristic of the patient and may therefore manifest itself, and in a variety of clinical forms, at any time from the cradle to the grave. In at least 15% of people this involves a major clinical problem, for the solution of which the intelligent coöperation of the patient is often indispensable. Such a book will be most helpful in making such coöperation possible. R. K.

THE ELECTROCARDIOGRAM IN CONGENITAL CARDIAC DISEASE. A Study of 109 Cases, 106 with Autopsy. By MAURICE A. SCHNITKER, B.Sc., M.D., Formerly Resident Physician, Peter Bent Brigham Hospital and Assistant in Medicine, Harvard University Medical School, Boston, etc. Pp. 147; 24 plates. Cambridge: Harvard University Press, 1940. Price, $3.00.

THIS monograph includes more than its modest title would suggest. For each of the important types of congenital heart disease, there is a discussion of the clinical picture and the abnormal physiology. An earnest attempt has been made to correlate these with the electrocardiographic pattern. The material referred to consists of 109 cases, all save three with necropsy confirmation. The fact that only one abnormality (congenital dextro-

cardia) produces an electrocardiogram pathognomonic of congenital heart disease, in no wise diminishes the value of this book for one interested in the subject. The Reviewer regrets that no mention has been made of changes which may occur in the chest leads. W. J.

MODERN DIABETIC CARE, Including Instructions in the Diet and the Use of the Old and New Insulins. By HERBERT POLLACK, A.B., PH.D., M.D., Instructor in Clinical Medicine, Cornell Medical College; Chief of Diabetic Clinic, Mt. Sinai Hospital, New York City, etc. Pp. 216; 13 illustrations. New York: Harcourt, Brace & Co., 1940. Price, $2.00.

THIS volume offers no particular advantages over several excellent manuals now available. It uniquely recommends that one-third to two-thirds of the daily protein be given at the evening meal in order to provide a source of slowly available glucose throughout the night. One chapter considers the problems peculiar to the diabetic: marriage, driving, legal responsibility, occupation, and diabetic costs. Written primarily for the patient, this volume suffers from lack of illustrations; the thirteen reproduced are entirely devoted to the handling of insulin. M. B.

PNEUMOCONIOSIS (SILICOSIS). The Story of Dusty Lungs. A Preliminary Report. By LEWIS GREGORY COLE, M.D., Director of Silicotic Research, John B. Pierce Foundation, New York City, and WILLIAM GREGORY COLE, M.D., New York City. Pp. 56 and Appendix (47 pages); illustrated. New York: John B. Pierce Foundation, 1940 Price, $1.00.

THIS small monograph is somewhat unusual. It might be described as being written in a "Colerian" style. Early in the monograph the Cole collaborators say that they have approached the study of pneumoconiosis in a manner that is not conventional. The authors describe four types of pneumoconiosis and give their reasons for their new terminology and their new classifications. The authors take issue with a number of the conventional ideas concerning silicosis and it is to be regretted that in this monograph they did not take more space to substantiate the position that they have taken concerning pneumoconiosis. One of the striking things about this monograph is the total absence of any bibliographic reference, yet throughout the text there are small numbers presumably referring to other articles published on this subject. E. P.

OBESITY AND LEANNESS. By HUGO R. RONY, M.D., Formerly Associate in Medicine and Chief of Endocrine Clinic, Northwestern University School of Medicine, Chicago; Formerly Attending Physician, Cook County Hospital, Chicago, Ill. Pp. 300; 32 illustrations. Philadelphia: Lea & Febiger, 1940. Price, $3.75.

THE delicate mechanism which controls the weight of most adults within narrow limits over a period of years has been estimated to adjust food intake and energy output to within 0.05%. This the author denotes as the "homeostatic weight regulation." In his emphasis on this nicety of balances, he diverges from the older conceptions of obesity as a disturbance of energy exchange. So far as the Reviewer is aware, the subject of leanness has not previously received extensive discussion. The volume is divided into three parts: I, A Synopsis of the Physiology of Fats and Fat Tissue, which has been called "a neglected tissue"; II, The Pathogenesis of Obesity and Leanness; and III, The Clinical Aspects of Obesity and Leanness. Modern researches on the endocrines, nervous system, and intermediary

metabolism pertaining to the problem are fully covered; speculations are carefully sifted, and short résumés are frequently appended. The lipophilia theory and a discussion of regional and segmental lipophilia are authoritatively considered. Danforth's work on the obesity of yellow mice and Davenport's data on the Mendelian inheritance of obesity receive appropriate attention. The author differs sharply with the "overeating" school and presents a relatively simple classification of both obesity and leanness. Eighty-six pages are devoted to the clinical aspects and practical details of treatment. This scholarly monograph merits the attention of investigators and should prove useful to the practicing physician.

M. B.

PNEUMONIA AND ITS NURSING CARE. By HERBERT K. ENSWORTH, B.S., M.D., and LELA GREENWOOD, R.N. Pp. 177; illustrated. Philadelphia: J. B. Lippincott Company, 1940. Price, $1.50.

A VERY comprehensive monograph that includes every aspect of medical and nursing care of the pneumonia patient today. The material for this simply written little book is based on a study of pneumonia made at Bellevue Hospital starting in 1922, financed by the Metropolitan Life Insurance Company, with additional aid from the Littauer Pneumonia Fund a few years later. In addition to the five or six hundred pneumonia patients cared for at Bellevue, other sources of information were studies made by other medical groups and articles from professional magazines, all of which are listed as references for further reading on each chapter. M.S.

THE ERA KEY TO THE U. S. P. XI AND N.F. VI. Fifth edition revised by LYMAN D. FONDA, Professor of Pharmacy, Brooklyn College of Pharmacy, Long Island University. Pp. 320. Newark, N. J.: The Haynes and George Company, Inc., 1940.

A CONVENIENT, practical, pocket-sized booklet that furnishes an epitome of the U. S. Pharmacopœia and the National Formulary, as well as information about many non-official preparations, incompatibilities, drug dosage, prescription terminology and the like. R. K.

COMPLETE GUIDE FOR THE DEAFENED. By A. F. NIEMOELLER, A.B., M.A., B.S. With a Foreword by HAROLD HAYS, M.D., F.A.C.S. Pp. 256. New York: Harvest House, 1940. Price, $3.00.

THIS guide contains concise and authoritative information, presented in terms the average layman can understand. Separate chapters deal with the relation of colds, diet, glands, drugs, sinusitis, tonsils, adenoids, teeth, and allergy to hearing. Every aspect of impaired hearing is covered. Occupational deafness, the relation between noise and deafness, and the effects of swimming upon the hearing are given adequate attention. Audiometers, audiograms and hearing aids are explained in simple terms. Proper emphasis is placed upon re-education of residual hearing, and lip reading. The importance of voice and speech culture for the hard of hearing is demonstrated, while directions are also given for more effectively hearing the radio, conversation, the telephone and public speakers. The addition of an index will render subsequent editions more useful. This volume should be read by every deafened individual, not alone for its wealth of information (which the busy otologist only too often fails to give the patient), but also because of the understanding and sympathetic approach to the problem of social and psychologic adjustment. Most otologists will benefit by a thorough perusal of this book. H. S.

PRINCIPLES AND PRACTICE OF AVIATION MEDICINE. By HARRY G. ARMSTRONG, B.S., M.D., Captain, Medical Corps, U. S. Army; Director, Aero Medical Research Laboratory, Air Corps Materiel Division. Pp. 504; 89 illustrations. Baltimore: The Williams & Wilkins Company, 1939. Price, $6.50.

THAT a new specialty, Aviation Medicine, has arrived is amply attested by this timely and comprehensive volume, the first major textbook on the subject. The scope of the work is indicated by the titles of its 27 chapters: Historical; The Flight Surgeon; Evolution of Pilot Selection; Introduction to Pilot Selection; Examination of the Eye; Cardiovascular Examination; Ear, Nose and Throat; General Physical Examination; Neuropsychic Examination; Care of the Flier; Noxious Fluids and Gases; Wind, Ventilation, Cold, Heat, Light and Vibration in Flight; Effect of Flight on the Ear; Aerial Equilibration and Orientation; Airsickness; Anoxia; Acute Altitude Sickness; Chronic Altitude Sickness; Oxygen in Aviation; Psychology of Flight; Protective Flying Equipment; Aerial Relief and Sanitation. The book has been written primarily as a textbook for students and as a reference work for those actively engaged in the practice of aviation medicine. It should, however, find a much wider appeal. Written in an easy interesting style, it tells a fascinating story of the important and indispensable part that medical research has played in the development of flying. All physicians as well as scientifically minded laymen will find this volume as enjoyable reading as any best-seller. Moreover, physicians will be surprised to find much information of practical value in general medical practice, notably from the standpoint of advice to would-be airplane passengers among their patients. The book is enthusiastically recommended to all medical readers. R. K.

A MANUAL OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY. By HOWARD CHARLES BALLENGER, M.D., F.A.C.S., Assistant Professor of Otolaryngology, Northwestern University School of Medicine, Chicago. Pp. 302; 90 illustrations and 4 color plates. Philadelphia: Lea & Febiger, 1940. Price, $3.75.

BASED upon the more comprehensive Ballenger's "Diseases of the Nose, Throat and Ear," this volume presents a more concise textbook by omitting theories and surgical technique while emphasizing anatomy, etiology, symptoms and treatment. It provides an adequate and reasonably priced text for undergraduate instruction, with sufficient brevity to conform to the recent trend in undergraduate teaching of the specialties. These attributes, admirably adapted to the author's purpose, render the volume inadequate as a reference work for the general practitioner and otologist. H. S.

PRECLINICAL MEDICINE: Preclinical States and Prevention of Disease. By MALFORD W. THEWLIS, M.D., Attending Specialist, General Medicine, U. S. Public Health Hospitals, New York City; Specialist Consultant, Rhode Island Department of Public Health; Associate Editor, Medical Times. Pp. 223; 12 illustrations. Baltimore: The Williams & Wilkins Company, 1939. Price, $3.00.

"PRECLINICAL Medicine is that branch of medicine which ascertains disease conditions which are likely to occur, such as peptic ulcer, osteoarthritis, especially the degenerative diseases. It lies wholly within the field of preventive medicine." It aims at the comprehensive diagnosis and preventive treatment of preclinical states by considering the individual as a whole, including his heredity, constitutional type, social as well as physical environment. The experienced general practitioner is not only the best prepared to work in this field, but also the one who should particularly interest

himself in it. The subject matter is presented in four sections, including (1) general considerations of history, constitution and examination, (2) specific infectious diseases, (3) non-infectious diseases (occupational diseases, diet, allergy, alcoholism), and (4) pathologic possibilities in the various parts of the body (*e. g.*, heart and blood-vessels, alimentary tract, respiratory tract and others). The chief value of the book is its viewpoint, which is deserving of the fullest consideration by physicians. The chief criticism of the book is its failure adequately to cover so broad a subject within its too limited size. R. K.

NEOPLASTIC DISEASES. A Treatise on Tumors. By JAMES EWING, A.M., M.D., SC.D., LL.D., Professor of Oncology at Cornell University Medical College, New York City; Consulting Pathologist, Memorial Hospital. Pp. 1160; 581 illustrations. Fourth edition, revised and enlarged. Philadelphia: W. B. Saunders Company, 1940. Price, $14.00.

THE fourth edition of this great work arrives opportunely. The past 10 years have witnessed notable progress in our knowledge of neoplastic diseases, with contributions from physics, chemistry, genetics, physiology and pathology. To sift the grain from the chaff in the tremendous volume of literature thus accumulated is a momentous undertaking. The author has done this. It is, as would be expected, mainly in the section on General Oncology that most of the new material finds its place. For instance, in the chapter on Experimental Cancer Research, the work of Cook, Dodds and Hewett on carcinogenic hydrocarbons, and the chemical relationship of these compounds to hormones is included. The inclusion of new material has been accomplished without apparently increasing the size of the volume, by omitting matter of mainly historical interest, together with some controversial subjects. The book has lost none of its original value as a comprehensive survey of the neoplastic diseases; it has been brought up to date without departure from its sound and sober attitude. The fourth edition should only further increase the popularity gained by the preceding editions. D. C.

NOTES ON THE PREPARATION OF PAPERS FOR PUBLICATION in The Journal of Hygiene and Parasitology. By the Late G. H. F. NUTTALL, M.D., SC.D., PH.D., LL.D., F.R.S., Lecturer in Bacteriology (1900–06) and Lecturer in Biology (1906–31) in the University of Cambridge, Founder and Editor (1901–37) of the "Journal of Hygiene" and Founder and Editor (1908–33) of "Parasitology." Pp. 62. Cambridge: University Press, 1940.

MEDICAL papers as they come to the editor are of three kinds: (1) Papers that have something to say and say it very well; these, all too rare, are accepted by return mail. (2) Papers that have nothing to say and say it very badly; their rejection is a pleasure. (3) Papers that have something to say, but say it very badly; they are the chief cause of editorial headache. They remind him that he really ought to write that book on the preparation of medical papers, but he puts it off, pleading the pressure of work and the pessimistic thought that those who need it most would not read it, anyway. Even Dr. Nuttall never quite got around to it in nearly 40 years of editorship, but contented himself with making voluminous notes of the advance which he gave to inexpert authors. After his death, Drs. G. S. Graham-Smith and D. Keilin, his successors as editors, selected and edited those of his notes which seemed likely to be most useful to many authors. The result is a little book which most writers of medical papers (and most editors) could and should read with profit. R. K.

HANDBOOK OF HEARING AIDS. By A. F. NIEMOELLER, A.B., M.A., B.S. Foreword by HAROLD HAYS, M.D., F.A.C.S. Pp. 156. New York: Harvest House, 1940. Price, $3.00.

CONTAINING a maximum of information in a minimum of space, this volume considers all types of hearing aids. It presents concise and specific information concerning the principles of operation, advantages and disadvantages, efficiency and cost of each instrument. Frank discussion and unbiased criticism enable the deafened individual to sift the maze of conflicting claims made by competing manufacturers and, with the aid of the otologist, to select the hearing aid best suited to his type of disability and to his purse. H. S.

SPECIALTIES IN MEDICAL PRACTICE (NELSON LOOSE-LEAF). Edited by EDGAR VAN NUYS ALLEN, M.D., Chief of a Section in the Division of Medicine, The Mayo Clinic, Rochester, Minnesota; Associate Professor of Medicine, The Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota. With a Foreword by DONALD C. BALFOUR, M.D., F.A.C.S., F.R.C.S. (ENG.), F.R.A.C.S., Consultant in Surgery, The Mayo Clinic; Professor of Surgery and Director, The Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota. Two Volumes. Pp. 964; 264 illustrations, 7 color plates. New York: Thomas Nelson & Sons, 1940. Price, $25.00.

A SERIES of monographs by specialists to give such information in their respective fields as will meet the needs of the general practitioner. Subjects covered and writers are ophthalmology (Harry S. Gradle, Chicago), diseases of the ear, nose and throat (Lawrence R. Boies, Minneapolis), neurology (Henry R. Viets, Boston), psychiatry (Lloyd H. Ziegler, Milwaukee), the vitamins and vitamin deficiency diseases (Dwight L. Wilbur, San Francisco), allergy (Frank A. Simon, Louisville), orthopedic surgery (Don King, San Francisco), obstetrics and gynecology (G. D. Royston, St. Louis), endocrinology (William O. Thompson, Chicago), urology (John L. Emmett, Rochester, Minn.), and proctology (Louis A. Buie, Rochester, Minn.). A chapter on dermatology and syphilology is in preparation. The idea behind such a work is an excellent one, and it has been well carried out. The authors have largely avoided the mistake of including material involving techniques with which the practitioner should not concern himself. An exception is the section on proctology, with its descriptions of a number of formidable operative procedures. The loose-leaf principle, permitting of periodic accessions and revisions, has obvious advantages. Its chief disadvantage, excessive cost of additional material, has been minimized by the publishers, in that, instead of charging a flat yearly service fee, they offer the added material at the rate of 2 cents a page. The work should find a wide appeal. R. K.

NEW BOOKS

Biochemistry of Disease. By MEYER BODANSKY, PH.D., M.D., Director of the John Sealy Memorial Laboratory and Professor of Pathological Chemistry, University of Texas School of Medicine, and OSCAR BODANSKY, PH.D., M.D., Lecturer in Biochemistry, Graduate Division, Brooklyn College, etc. Pp. 684; 72 illustrations. New York: The Macmillan Company, 1940. Price, $8.00.

Endocrine Therapy in General Practice. By ELMER L. SEVRINGHAUS, M.D., F.A.C.P., Professor of Medicine, University of Wisconsin, etc. Pp. 239; 49 illustrations. Chicago: The Year Book Publishers, Inc., 1940. Price, $2.75.

Surgery of the Hand. (Wounds, Infections and Closed Traumata). A Book for the Practitioner and the Surgeon. By MARC ISELIN, M.D., Surgeon, The American Hospital, Paris. Translated by T. M. J. d'OFFAY, M.B., CH.B. (EDIN.), F.R.C.S. (ENG.), Surgeon and Deputy Medical Superintendent, City General Hospital, Leicester, and THOMAS B. MOUAT, M.D., CH.M. (EDIN.), F.R.C.S. (ENG.), Surgeon, The Royal Infirmary, Sheffield, Lecturer in Surgery, The University of Sheffield. Pp. 353; 135 illustrations, including 8 plates. Philadelphia: The Blakiston Company, 1940. Price, $5.50.

The Head and Neck In Roentgen Diagnosis. By HENRY K. PANCOAST, M.D., Late Professor of Radiology and Director of the Department of Radiology, University of Pennsylvania, EUGENE P. PENDERGRASS, M.D., Professor of Radiology and Director of the Department of Radiology, University of Pennsylvania, and J. PARSONS SCHAEFFER, M.D., PH.D., Professor of Anatomy and Director of the Daniel Baugh Institute of Anatomy, Jefferson Medical College. Pp. 976; 1251 illustrations. Springfield, Ill.: Charles C Thomas, 1940. Price, $12.50.

Simplified Diabetic Manual with 163 International Recipes (American, Jewish, French, German, Italian, Armenian, etc.). By ABRAHAM RUDY, M.D., Associate Physician and Chief of the Diabetic Clinic, Beth Israel Hospital, Boston; Instructor in Medicine, Tufts College Medical School, etc. Introduction by DR. FREDERICK M. ALLEN. Pp. 216; illustrated. New York: M. Barrows & Co., Inc., 1940. Price, $2.00.

Pneumonia and Its Nursing Care. By HERBERT K. ENSWORTH, M.D., Instructor in Medicine, Cornell University Medical College; Clinical Assistant Visiting Physician, Second (Cornell) Medical Division, Bellevue Hospital, New York City, and LELA L. GREENWOOD, B.A., R.N., Supervisor of Medical Pavilion, Bellevue Hospital, New York City; Assistant Instructor, Department of Therapeutics, New York University Medical College. With a Foreword by RUSSELL L. CECIL, M.D. Pp. 177; illustrated. Philadelphia: J. B. Lippincott Company, 1940. Price, $1.50.

Health is Wealth. By PAUL DE KRUIF. Pp. 246. New York: Harcourt, Brace & Co., 1939. Price, $2.00.

The Emperor's Itch. The Legend Concerning Napoleon's Affliction with Scabies. By REUBEN FRIEDMAN, M.D., Assistant Professor of Dermatology and Syphilology, Temple University School of Medicine, Philadelphia. Pp. 89; 10 illustrations. New York: Froben Press, 1940. Price, $1.50.

Immune-Blood Therapy of Tuberculosis. With Special References to Latent and Masked Tuberculosis. By JOSEPH HOLLOS, M.D. Pp. 195. Boston: Bruce Humphries, Inc., 1938. Price, $2.50.

Dermatologic Therapy in General Practice. By MARION B. SULZBERGER, Assistant Clinical Professor of Dermatology and Syphilology, Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital of Columbia University; Associate Attending Dermatologist, Montefiore Hospital, New York City, and JACK WOLF, M.D., Attending Dermatologist and Syphilologist, Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital of Columbia University, Director of Dermatology, New York City Cancer Institute. Pp. 680; 65 illustrations and 25 tables. Chicago: The Year Book Publishers, Inc., 1940. Price, $4.50.

La Maniobra ano Parieto-Abdominal en el Estudio de los Procesos Agudos del Abdomen. Su contribución semiológica, clinica diagnóstica y pronóstica. By DR. EMILIO S. SAMMARTINO. Pp. 110; 2 illustrations. Buenos Aires: "El Ateneo," 1940.

Quarterly Journal of Studies on Alcohol, Vol. 1, No. 1, June, 1940. HOWARD W. HAGGARD, M.D., Editor. Pp. 200. New Haven: Quarterly Journal of Studies on Alcohol, 1940. Price, $1.00 single copy; $3.00 annually.

Notes on the Preparation of Papers for Publication in The Journal of Hygiene and Parasitology. By the Late G. H. F. NUTTALL, M.D., Sc.D., PH.D., LL.D., F.R.S., Lecturer in Bacteriology (1900–06) and Lecturer in Biology (1906–31) in the University of Cambridge; Founder and Editor (1901–37) of the "Journal of Hygiene" and Founder and Editor (1908–33) of "Parasitology." Pp. 62. Cambridge: University Press, 1940. (Review, p. 408.)

Gynecological and Obstetrical Pathology. With Clinical and Endocrine Relations. By EMIL NOVAK, A.B., M.D., D.Sc. (HON. DUBLIN), F.A.C.S., Associate in Gynecology, The Johns Hopkins Medical School; Gynecologist, Bon Secours and St. Agnes Hospital, Baltimore, etc. Pp. 496; 427 illustrations. Philadelphia: W. B. Saunders Company, 1940.

Physiology of Micturition. Experimental and Clinical Studies with Suggestions as to Diagnosis and Treatment. By ORTHELLO R. LANGWORTHY, LAWRENCE C. KOLB and LLOYD G. LEWIS. Sub-Department of Neurology and James Buchanan Brady Urological Institute, The Johns Hopkins University. Pp. 232; 49 illustrations. Baltimore: The Williams & Wilkins Company, 1940. Price, $3.50.

Clinical Practice in Infectious Diseases. For Students, Practitioners and Medical Officers. By E. H. R. HARRIES, M.D. (LOND.), M.R.C.P., D.P.H., Medical Superintendent, Northeastern Hospital (London County Council), etc., and M. MITMAN, M.D. (LOND.), M.R.C.P., D.P.H., D.M.R.E., Medical Superintendent, River Hospitals, etc. With a Foreword by W. ALLEN DALEY, M.D. (LOND.), F.R.C.P., D.P.H., Medical Officer of Health, London County Council. Pp. 468; illustrated. Baltimore: The Williams & Wilkins Company, 1940. Price, $6.00.

NEW EDITIONS

A Textbook of Histology. By HARVEY ERNEST JORDAN, A.M., PH.D., Professor of Anatomy and Director of the Anatomical Laboratories, University of Virginia. Pp. 690; 609 illustrations. Eighth edition. New York: D. Appleton-Century Company, 1940. Price, $7.00.

The Era Key to the U. S. P. XI and N. F. VI. Revised by LYMAN D. FONDA, Professor of Pharmacy, Brooklyn College of Pharmacy, Long Island University. Pp. 320. Fifth edition. Newark, N. J.: The Haynes & George Company, Inc., 1939. (Review, p. 406.)

Green's Manual of Pathology. Revised and enlarged by H. W. C. VINES, M.A., M.D., Director of the Charing Cross Hospital Institute of Pathology. Pp. 1166; 701 illustrations. Sixteenth edition. Baltimore: The Williams & Wilkins Company, 1940. Price, $8.50.

Histopathology of the Peripheral and Central Nervous Systems. By GEORGE B. HASSIN, M.D., Professor of Neurology, University of Illinois, College of Medicine, Attending Neurologist, Cook County Hospital, Chicago. Pp. 554; 302 illustrations. Second edition, revised and enlarged. New York: Paul B. Hoeber, Inc., 1940. Price, $7.50.

PROGRESS
OF
MEDICAL SCIENCE

PREVENTIVE MEDICINE AND EPIDEMIOLOGY.

UNDER THE CHARGE OF

JOHN E. GORDON, M.D.

PROFESSOR OF PREVENTIVE MEDICINE AND EPIDEMIOLOGY, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS.

THE EPIDEMIOLOGY OF MUMPS.

With much of the world turned to war and the remainder variously engaged in recruiting military strength, epidemiology steps forward into obligations long associated with armed conflict. As a consequence, ordinary epidemiologic interests undergo appreciable and sometimes startling changes in emphasis. Typhus fever becomes a matter of unusual concern; memories of the 1918 pandemic of influenza are freshened; but most surprising of all to the uninitiated is the consideration given to mumps.

To the military surgeon, mumps is no passing indisposition of benign course but ranks with many of the more formidable diseases because of its frequent appearance in epidemic proportions, the high non-effective rate among army personnel brought about by the long indisposition, and because in young adults the associated manifestations of epidemic parotitis lead to a clinical course considerably more serious than when mumps is a disease of childhood. In summarizing the general problems that communicable disease presented in the war of 1918, Haven Emerson[18] stated that in terms of sick wastage, and measured by the number of days lost from military service on account of sickness, mumps was the most important disease in the American Expeditionary Force in France. Indicative that opinion has not changed in the course of years, is the recent statement of Surgeon General Parran,[66] of the United States Public Health Service, that next to the venereal diseases, mumps is the most disabling of the acute infections among recruits.

Aside from military considerations mumps warrants interest in its own right. The practicing physician, to be sure, is usually occupied with diseases of more serious course and higher fatality, so that mumps by more or less common consent is relegated with chickenpox, rubella, and some other infections to a group designated the minor communicable diseases. However, the biologist faces no distinction between

major and minor infections, and the epidemiologist often derives equal profit, in respect to the fundamental laws of behavior of communicable processes, from diseases that are common and benign.

The current interest in virus diseases has led to a number of studies on the specific infectious agent of mumps, with the result that the past few years have seen notable additions to what was known of the etiology, biologic nature, and mode of origin of this condition, with promise of more effective measures for clinical management and control.

The Clinical Disease. Mumps is such an old disease and so many good descriptions are available,[62,65] that the clinical aspects will be touched upon only insofar as they pertain to interpretation of the mechanism of the disease process.

The use of the term epidemic parotitis for statistical purposes and as descriptive of the disease is unfortunate, for it associates the condition too closely with changes in the parotid. The current edition of the International List of Causes of Death[39] catalogues the disease as mumps, which should bring about more general usage of a time-honored name favored by most clinicians and epidemiologists.

The clinical recognition of mumps is ordinarily so certain in comparison with many other infectious diseases that not much confusion is introduced into epidemiologic interpretations through inclusion of other forms of parotitis or conditions which simulate parotitis but are not inflammations of that gland. They furthermore occur so uncommonly as to have little influence on morbidity statistics. That is not true, however, of mortality rates. Mumps of itself is rarely a cause of death, but some of the conditions confused with it often end fatally.

Mumps is unattended by suppuration, but suppurative parotitis does occur in connection with septicemic and cachectic states, and in association with diseases such as typhoid fever and scarlet fever. The fatality in such instances is likely to be great, not so much because of the involved parotid but because of the primary condition. Postoperative swelling of the parotids, especially after surgical procedures involving the abdominal cavity, and symptomatic parotitis occurring toward term in pregnancy are not rare. A chronic recurrent form of parotitis is associated with diseases of the upper respiratory tract, like the recently reported instance[5] of a series of recurrent attacks of parotitis, one of which was mumps. Prolonged swelling of the parotid may be due to secondary infection after mumps, or in exaggerated instances and very rarely to Mikulicz's disease. An experience with 367 hospital admissions[25] for mumps is presented in Table 1.

Such a distribution would not be typical of private practice, since only the more severe and more difficultly determinable infections are ordinarily sent to hospital.

The development of knowledge about mumps falls readily into three periods. The first was concerned chiefly with the study of frank epidemics, and served to establish the communicability of the condition and its wide distribution. Hirsch's[37] collection of some 150 epidemics occurring between 1714 and 1859 showed the disease to be prevalent from Iceland to Egypt, and from Alaska to Polynesia. Accumulated evidence from outbreaks in the first half of the nineteenth century illustrated another epidemiologic feature of mumps, its predilection for prisons, orphanages, boarding schools, garrisons, and ships. The second

general advance was concerned with better definition of the clinical features of mumps for which especial credit is due the sustained interest of a brilliant line of French army surgeons. The third era was initiated with the production of mumps experimentally and the recognition of the specific infectious agent.

TABLE 1.—PATIENTS REFERRED TO HERMAN KIEFER HOSPITAL AS MUMPS, DETROIT, MICHIGAN, 1927–1937.

Disease.	Cases.	Incidence per 100 cases.
Mumps	310	84.5
Local suppurative processes of head and neck	27	7.4
Other infectious diseases with complications suggesting mumps	20	5.4
Suppurative parotitis	5	1.4
Symptomatic parotitis	3	0.8
Contusion of face	1	0.3
Mikulicz's disease	1	0.3

Etiology. The long series of bacteriologic investigations on saliva, blood and tissues from patients with mumps, starting with the early studies of Capitan and Charrin[7] and continuing for many years, led to the demonstration of various pyogenic cocci but to no satisfactory proof that they had anything to do with the production of the disease. They were ordinary mouth contaminants or the factors in secondary infection.

A spirochete reported by Kermorgant[44] to be the specific agent of mumps never received much credence. The parotitis produced in monkeys could not be transmitted in series. Pontano[68] found the suspected spirochete more often in normal saliva than in that from patients with mumps, and Rocchi[75b] proved it to be only a banal inhabitant of the buccal cavity.

The experiments of Granata[28] in 1908 gave the first suggestion that the cause of mumps was a filterable virus. Rabbits injected intravenously with bacteriologically sterile filtrates of saliva from patients suffering from mumps had fever over a period of 3 days. Direct inoculation of the parotid glands of rabbits with filtered saliva gave rise to a swelling considered to be mumps, but the many subsequent failures to produce experimental mumps in the rabbit suggest the interpretation to have been erroneous.

Nicolle and Conseil[61] in 1913 injected fluid aspirated from the parotid gland of a patient with mumps, directly into the parotids of several monkeys. One animal developed what was considered a typical swelling of the gland, accompanied by fever and a monocytosis of the blood.

Four of the 10 monkeys that Gordon[26] injected intracerebrally with bacteria-free filtrates of mumps saliva developed meningeal symptoms on the fourth day and died. Necropsy showed a sterile lymphocytic meningitis, but attempts to transfer the infection to other monkeys were unsuccessful. An additional monkey inoculated intraperitoneally and intravenously became ill after an incubation period of 7 days and showed swelling of the parotid glands.

With filtered mouth washings from patients with mumps, Wollstein[99a,b] inoculated directly the parotid glands of half-grown cats, producing a swelling resembling mumps in man after an incubation

period varying from 5 to 8 days. The condition was reproduced in series. The virus was obtained most readily from the saliva of patients in the first 3 days of the disease, less readily on the sixth day, and not at all on the ninth. It was present in the blood of patients having marked constitutional effects. A mild aseptic meningitis of 3 to 5 days' duration,[99c] and transmissible in series, was induced by intrathecal injection of filtered saliva from early mumps, while sterile saliva from normal persons gave no reaction.

Complete and convincing demonstration that the infectious agent of mumps is a filterable virus came in 1934. Johnson and Goodpasture[43a] injected into the lumen of Stenson's duct of monkeys a fresh untreated saliva from patients in the early stages of the disease. Acute non-suppurative parotitis, analogous to that of mumps in man, and dependent histologically on a primary degeneration and necrosis of the parenchyma cells of the parotid, followed 4 of 6 attempts, the 2 failures being with saliva taken on the third day and later. Filtered mumps saliva had the same effect, although the incubation period was somewhat longer than the 6 to 8 days observed with unfiltered material. Recovery from the experimental infection conferred immunity to reinoculation for at least 3 months. The saliva of persons without mumps produced no disease. Since the materials used were free from demonstrable microorganisms, including spirochetes, they believed the causative agent of mumps to be a filterable virus.

Appreciating that final proof of causal relation must depend on production of the specific disease in the natural host with virus from the experimental disease, experiments were undertaken with 17 volunteers,[43b] children living in a small town, 4 of whom were presumably immune and 13 susceptible to mumps, with none known to have been recently exposed to the disease. The virus, in a suspension of minced parotid gland from the eleventh monkey of a passage series, was sprayed on the buccal mucosa and instilled into the nostrils, this being repeated the following day. The 4 immune persons were unaffected. Six of the 13 supposedly susceptible children developed clinical mumps, 3 had doubtful infections, and 4 failed to react. Saliva from one of the definite infections produced non-suppurative parotitis in a monkey. The incubation period for experimental mumps of man was, however, from 18 to 33 days in contrast to the 6 to 8 days in the monkey where virus was instilled directly into the parotid duct. These experiments established the cause of mumps to be a filterable virus, which now has been passed in monkeys through 35 generations in 3 years.

Important confirmation came from Findlay and Clarke[20] in England, who initiated the disease in monkeys with filtered mumps saliva and passed the virus in series with production of typical experimental mumps. Observation of suggestive virus particles by fluorescence microscopy in smears from the nose and throat of mumps patients contributed little evidence one way or the other.[84] In France a simple and rapid method was developed for collecting appreciable amounts of saliva directly from the opening of Stenson's duct.[81] Levaditi and his associates[54] also produced experimental parotitis in monkeys and in the chimpanzee, and confirmed their results histologically. Transmission in series was accomplished, but with some difficulty. No effect followed intravenous injection of filtered mumps saliva nor instillation

of the material into the nasal fossæ of monkeys. Contact of an infected chimpanzee with a healthy animal did not serve to transmit the disease. Because the experimental infection remained localized in the single parotid injected, since signs of a general infection were indefinite, and because similar histologic changes although of lesser degree were believed to occur after injection of presumably inert and non-specific substances, the French workers held certain reservations about the demonstration of a definite and constantly active virus, although agreeing that some element in the saliva of mumps could be transmitted in series through monkeys with the production of non-suppurative parotitis.

The real difficulty came from the fact that the histologic changes taking place in man in the course of mumps are not known definitely. Death from mumps is rare, necropsies still fewer,[48,93] and biopsies most infrequent. Occasional records such as those of Delater[14] caused Levaditi to remark, however, that the lesions of experimental mumps corresponded remarkably with the changes which had been noted in the human. Rocchi[75a] has reviewed current information about the histopathology of mumps in man, and Johnson and Goodpasture[43d] described in detail the pathologic changes of experimental mumps. Whether the lesions of experimental parotitis produced by injection of mumps filtrates into Stenson's duct of monkeys are microscopically specific, or are non-specific and reproducible by the injection of various other substances is capable of experimental proof; which Bloch[2] proceeded to acquire by showing the fundamental lesion of experimental mumps to be a focal acinar necrosis involving all or most of the cells of an acinus, a reaction not associated with injection of inert or other infectious substances.

Pathogenesis. With mumps demonstrated to be a virus disease and with an acceptable method for its production experimentally, there is opportunity for an improved understanding of the pathogenesis and biologic nature of the disease. A goodly amount of desirable information is still not at hand, but sufficient exists for examining the situation in the light of current developments, and for correlating much information of more remote origin, possible now of other interpretation than sometimes originally made.

The first and probably today the most commonly entertained conception of mumps is that of a primary local disease of the parotid which arises from invasion of the buccal cavity, progression of the infectious agent along Stenson's duct and eventual production of a non-suppurative swelling of the gland. The less common clinical manifestations of mumps such as orchitis, oöphoritis, pancreatitis, and the disturbances of the central nervous system, are thought to be complications of the primary disease brought about through occasional penetration of the agent into the blood or lymph stream.

Others regard mumps as a general rather than a localized process, with entrance of the virus by nose or mouth, lodgment on the mucous membranes of the nasopharynx probably, penetration to the blood stream and thereafter localization in various glandular structures, especially the parotid; and sometimes also in the central nervous system through successful penetration of the blood-brain barrier.

More recently has come the concept of Philibert[67] that mumps is due to a virus both cytotropic and neurotropic and comparable to that

of rabies; that it penetrates the host tissues by some unknown route, possibly the conjunctivæ; and electively gains entrance to the brain, provoking secondarily more or less reaction of the meninges. The virus being of low virulence, only slight and transient lesions are ordinarily produced; if more active, the virus may accomplish destruction of the nerve cells, giving rise to clinical encephalitis and occasionally paralyses. The virus is subsequently eliminated by the salivary glands, perhaps by nerve pathway, with swelling and partial destruction of the parotid; by the pancreas; or passes within the testicle which it often destroys in part; or into the kidney or other structures. Mumps is thus visualized as a primary disease of the central nervous system followed by secondary localization in salivary glands, pancreas, and testicle.

Since a satisfactory understanding of pathogenesis has so direct a bearing on programs for control, evidence will now be sought from known facts about the mechanism of spread of this filterable virus, from the immunity reactions which follow infection, from the clinical behavior of the disease, and from the studies of experimental mumps, in support of one or other of the concepts just stated.

Spread of the Virus. The sole reservoir of mumps infection appears to be man. An occasional reference to the natural disease in the dog[69] receives no confirmation from attempts to transmit infection from animal to animal by contact, or from man to animal. Experiments have invariably failed even with the chimpanzee,[54] and common epidemiologic knowledge discounts more than the accidental occurrence of such an event.

Mumps Carriers. Whether the human reservoirs of infection are limited to persons manifestly ill, or whether latent and subclinical infections also have a part, rests on no certain evidence. Practical experience in epidemics would indicate that latent infection with production of the temporary carrier state[24] is a factor, an impression also held by Zinsser.[101] Understanding subclinical infection to indicate disease with minimal clinical reaction and always measurably below recognized classical manifestations, such instances have been reported many times as far as the parotitis is concerned; in the form of slight tenderness at the angle of the jaw or slight redness at the orifice of Stenson's duct in association with mumps encephalitis.[94] Conceivably, the same situation could exist independently of other localizations, remaining wholly unrecognized as mumps infection.

Evidence of another kind comes from field surveys of history of previous attack by communicable disease[33,86] in general populations. Mumps occupied a somewhat intermediate position—64%[10a]—between measles, which had affected more than 89% of persons by age 20 years, and diphtheria with 10%, the latter a disease with a definitely known carrier factor in its epidemiology. Annual case rates adjusted for age[10b] show the same relationships[10c] between these diseases. The basic data about mumps would be expected if anything to be more accurate than those for measles. With no reason to believe that the two viruses are not equally widespread, one explanation of the difference in case rates could be the frequency of manifest disease as distinguished from latent or subclinical infection.

Mode of Transmission. The usual method of transmission is by direct contact and probably by droplet infection with perhaps occasional

instances where mumps results from oral contact with an article recently contaminated with the saliva of a patient with mumps.[95c]

Portal of Entry. The principal portal of entry would seem to be by way of the mouth or nose. Johnson and Goodpasture[43b] have produced mumps in man experimentally by spraying the virus on the mucosa of the upper respiratory tract; while Philibert's[67] suggestion of entrance by the conjunctivæ is wholly speculative. Whether the virus thereafter proceeds directly by way of the parotid duct or penetrates the mucosa to reach the parotid indirectly by the blood or by nerve trunks is not known. Angina frequently marks the early stages of the infection,[60] this condition often being overlooked because it ends at about the time that parotitis appears. This has been interpreted as the first localization of the virus.

Experimental mumps of monkeys[43a] after instillation of the virus directly into the duct had an incubation period of 6 to 8 days. The same virus after 11 passages in monkeys had an incubation period of 18 to 33 days when sprayed on the mucosa of the upper respiratory tract of man. With allowance for differences in host species and a possible attenuation of the virus by animal passage this would suggest that direct infection by the duct was an effective but probably not the natural method of infection, which if indirect would presumably involve a longer incubation time.

Examining histologically a piece of tissue from the parotid of a child in the third day of mumps, de Lavergne, Kissel, and Leichtmann[53] found no evidence of an ascending infection and inclined to the belief that infection was descending and came to pass by way of vessels or nerves.

Period of Infectiousness. Drawing on his own experience and a meticulous review of the literature, Wesselhoeft[95b] came to the conclusion that the usual incubation period of mumps was 18 days, with considerable variation from this mean in both directions. Orr[64] found a periodic fluctuation in numbers of cases every 18 days through 6 successive waves in an army outbreak in England; and thus another kind of evidence suggests that 18 days is about the correct period.

The incubation period is not wholly innocuous, for mumps becomes communicable some 48 hours before swelling of the parotid[55] is noted, and about 24 hours in advance of the first symptoms, at which time it reaches its height. Johnson and Goodpasture[43a] were unable to find virus in the saliva after 3 days of mumps, Wollstein[99b] in some few instances on the sixth day, but not on the ninth. This information is the guide to more logical regulations for isolation and quarantine than are now often prescribed.

Communicability. Field experience indicates that a rather solid contact is necessary for contracting the infection of mumps, such as that between members of a household or repeated and close contact under other situations. As with all communicable diseases, a number of epidemiologic considerations influence the degree of communicability; but by and large, given approximately equal and similar conditions, mumps is a good deal less communicable than measles and chickenpox, is less communicable than whooping cough, and much more communicable than scarlet fever and diphtheria.

Immunity. The resistance conferred by an attack of mumps is usually life-long and is just as enduring after unilateral as after bilateral parotitis, the prevalent notion to the contrary notwithstanding.[95c] Information from experimental mumps of the monkey[43c] corroborates this clinical experience, in that parotitis of one side invariably gives immunity to subsequent inoculation of the opposite gland, indicating that immunity is general and not local. Nevertheless, repeated attacks of mumps have been reported and in some instances may involve the side opposite the first.

Anyone experienced in communicable disease hospital practice appreciates the considerable error in histories of common communicable diseases of childhood, both in respect to diseases that persons have had and those that they have not had. If second attacks of mumps be limited to instances where both attacks were seen by a competent observer and if confusion with suppurative parotitis is eliminated,[5] second and recurrent attacks would be found not very common. Second attacks are expectedly more frequent in army practice where the elapsed time between attack in childhood is long, where the degree of exposure is great, and because of such general factors as stress and crowding and perhaps a carrier factor not otherwise materially pertinent.

A significant feature of Johnson and Goodpasture's[43c] studies on experimental immunity in the monkey was the demonstrated existence of subclinical and latent infections and their activity in producing immunity. Clinical mumps never followed spraying of the virus into the oral cavity of monkeys, but a solid immunity was frequently demonstrated thereafter as tested by direct inoculation of the virus into the parotid duct, a process which regularly induces mumps in the susceptible animal. A single injection intracerebrally was regularly followed by immunity, although clinical evidence of cerebral or meningeal disease was wholly absent and the virus could not be passed in series. Attempts to immunize monkeys passively to subsequent intraparotid injection of virus showed human convalescent serum to possess some weak antiviral action, but the experiments lacked preciseness because of readily appreciated technical difficulties. In general, the monkey appears relatively more resistant to the virus of mumps than is man.

Clinical Considerations. Turning now from those features of the spread of the virus in nature and the immunity reactions which follow natural and experimental infection, as they bear on the question of pathogenesis, the clinical behavior of the disease itself will be examined in the search for further evidence about the manner in which mumps develop.

Mumps is, of course, a good deal more than a simple disease of the parotid glands. The involvement of the associated salivary glands, the gonads, the pancreas, the central nervous system especially, and a number of other structures, including the special senses, has been recognized for many years and adequately described. The frequency with which these conditions occur is well illustrated by the recent reports of Janbon[41a,b,42] and many others. Their place in the pathogenesis of the disease is not so well established, being variously interpreted as complications following parotitis; a part of a general infection of which parotitis is only another manifestation; as capable of inde-

pendent existence; or that some one of them represents the primary disease to which the others, including parotitis, are secondary.

Time and Frequency Distribution. The weight of clinical evidence assures that, with rare exceptions, only the mature testis and ovary are involved in mumps infections. The frequency of orchitis among mumps patients past puberty is appreciably great—from the earlier review of Wesselhoeft[95a] and the more recent summary by Stengel,[85] in the nature of 18%. While orchitis usually follows parotitis and is more often unilateral than bilateral, there can be no doubt from the observations of many clinicians that it can also precede the appearance of parotitis, occur simultaneously, or exist as the sole clinical manifestation. The origin of the manifestation is probably hematogenous.[85] As long ago as 1899, Edwards[17] reported 4 patients with primary involvement of the testis, of whom 3 later had parotitis and 1 did not. Waddelow[91] records primary epididymitis in mumps. Wesselhoeft[95a] collected 30 reports of orchitis preceding parotitis, and no less than 64 cases of orchitis without parotitis; and increasing numbers have been added since the date of his review.

Ohlmacher[63] describes the much rarer circumstance of oöphoritis preceding parotitis. A laparotomy performed on the third day of an acute illness revealed a normal appendix, but the right ovary was considerably enlarged in comparison with the left, and presented a few minute petechiæ. Three days after operation the young woman developed a typical double parotitis of mumps.

Pancreatitis is only an occasional, or at least a much less commonly recognized effect in the course of mumps,[34] although Greene and Heeren[29] found 7 in their series of 100 young adults with mumps. The important consideration is that it follows the same pattern of behavior[3,9,87] as does involvement of the gonads, in that it may precede, accompany, or follow the swelling of the salivary glands.

No good statistical information is available concerning the frequency of encephalitis as a manifestation of mumps in a general population. The numbers in many series are too small for satisfactory judgment. Other groups represent selected ages, commonly young adults, and especially soldiers; and some data were collected at a time when clinical appreciation of the condition had not reached its present level. Indicative of reported experience under military conditions is a frequency of 9.8% in Dopter's[15] French army series of 1910 and 1911; to be compared with the single case of encephalitis among 5756 mumps patients at Camp Wheeler[71] in 1918. In a civilian outbreak of some 2500 cases[80] in Portland, Oregon, the frequency of encephalitis was 0.6%, while Steinberg[83] reports an incidence of 10% for 210 cases.

When encephalitis appears as a part of the picture of mumps it is usually as an aftermath of parotitis,[59] at varying intervals of 2 to 10 days. Outspoken involvement of the central nervous system as the initial manifestation of mumps infection, to be followed later by parotitis, is no unusual occurrence, Silwer[77] having collected a series of 21 such cases. The recent report of Gasser[22] is particularly informative because mumps encephalitis was observed in its full period of development before parotitis, the patient having been under hospital observation for a traumatic injury. Sometimes encephalitis and parotitis develop concurrently.[47]

The Occurrence of the Several Manifestations of Mumps as Independent Processes. The great preponderance of clinical mumps has parotitis as the sole manifestation. If the other clinical conditions that make up the total disease have parity with parotitis as evidences of secondary localization after an initial general infection—presumably of the blood—or after some other primary localization, then the expectancy is that in some instances each will also exist independently of the others, as does parotitis. Accumulated clinical experience shows this to be true. Orchitis presumably of mumps origin and without an associated parotitis is a matter of long observation.[95a] Similarly, encephalitis independent of other manifestations of mumps has been reported by Howard,[38] and by Wallgren,[92] among others, while Wesselhoeft[95c] offers evidence of like behavior in respect to pancreatitis. Identification as of mumps origin has invariably depended upon clinical and epidemiologic evidence, since the virus of mumps has never been isolated under such circumstances, other than from parotitis.

Evidence of a General Infection. The appearance of a swollen parotid may be the first accident in the course of well-being, but more frequently swelling of the gland is preceded by functional and general signs of variable intensity which correspond to the beginnings of a general infection, Moutier[60] emphasizing especially a constant angina, and Greene and Heeren[29] the frequent occurrence of an enlarged spleen.

Latent Encephalitis. Philibert's[67] concept of mumps as a primary disease of the central nervous system evolved from the many clinical observations on the associated meningo-encephalitis. This condition invariably shows a well-marked pleocytosis of the cerebrospinal fluid. Many years ago, however, Monod[58] reported increased numbers of lymphocytes in the cerebrospinal fluid from 6 of 8 patients who had parotitis but no demonstrable signs of meningeal irritation whatsoever. Of 40 patients with mumps at the Willard Parker Hospital,[21] 10 with clinical encephalitis and 6 with only parotitis had cell counts that ranged from 15 to 880. That pleocytosis of the cerebrospinal fluid occurs in the absence of clinical signs is assured; the difference of opinion lies in its frequency, with estimates varying from an uncommon occurrence,[70] 5%,[8] the 25% of Teissier and Eismein,[62] to a constant presence as indicated by the results of de Massary[56a,b] and associates who routinely examined the cerebrospinal fluid of 56 soldiers with mumps, 40 having no clinical evidence of encephalitis. All showed increased numbers of lymphocytes some time during the course of the disease, although not always in the fluid drawn from the first puncture.

In an attempt to relate these disturbances to the virus of mumps, de Lavergne[51a,52] and associates injected filtered and unfiltered cerebrospinal fluid from patients with mumps encephalitis into the subarachnoid space of rabbits by suboccipital puncture. Essentially no clinical reaction followed, which was also true when the fluid was introduced into the parotid, the testicle, or the blood stream. However, the number of lymphocytes in the cerebrospinal fluid increased significantly, to be followed later by histologic evidence[51b] of a demyelinization of perivascular distribution. A variety of inert materials, including spinal fluid from other sources, failed to give these changes, nor did filtered saliva from non-mumps patients. Attempts to neutralize the supposed virus *in vitro* were unsuccessful, nor could active immunity

after one injection be determined. Moreover, the changes noted were almost invariably produced by cerebrospinal fluid from patients with simple mumps,[51a] in the complete absence of signs of encephalitis or cytochemical alteration of the spinal fluid. The cerebrospinal fluid of a number of persons was next examined 15 days[51c] after exposure to mumps, and 3 to 7 days before parotitis appeared. The typical reaction of the rabbit followed. Fluids from some of the contacts who failed to develop parotitis nevertheless produced the same reaction in the rabbit as did those who later developed the disease, suggesting an inapparent infection of the central nervous system as the only manifestation of mumps infection in man. de Lavergne and Kissel[50] believe these experiments bring support to the hypothesis of Philibert. The matter hinges on the soundness of the criteria considered indicative of the activity of a mumps virus. Experimental parotitis was never produced with the spinal fluid of patients or of infected rabbits.

Biologic Nature of Mumps. Drawing now on the various kinds of evidence which have been offered in an attempt to formulate a tenable explanation of the pathogenesis of mumps, it would appear that the portal of entry is by the nose and mouth,[43b] with lodgment of the mumps virus on the mucosa of the upper respiratory tract.[60] A variety of evidence, epidemiologic, clinical, immunologic and experimental, indicates mumps to be a general infection,[60] probably of the blood stream,[99a] and not a strictly local disease. In the localizations that follow the general infection, the virus manifests a special predilection for glandular structures of which the parotid is most often and first affected. With multiple structures involved, the parotid usually precedes all others, but sometimes this sequence is disturbed with striking effect on the timing of the disease, so that the testes, the central nervous system or the pancreas may be first invaded. The infrequent occurrence of clinical neurologic disease, the special selectivity of the virus for glandular tissues, and the preponderance of encephalitis over meningeal reaction suggest that if this part of the disease is related to the virus of mumps it comes about through passage of the agent through the blood-brain barrier. It is not necessary, of course, to assume that the march of the disease follows one route only. The three possibilities noted may all act, but the evidence suggests that just outlined as usual.

That mumps is a primary disease of the central nervous system is an interesting hypothesis. Certain clinical features are suggestive.[11] Histologically Johnson and Goodpasture[43c] found some evidence that infection of nerve tissue after intracranial injection of monkeys may spread by nerve to the otic ganglion and possibly the parotid—at the same time emphasizing the need for further experiment. However, a direct relation between the virus of mumps and the naturally associated encephalitis has not been established.

Endemicity and Epidemicity. Mumps is an endemic disease in general urban populations, but subject to irregular fluctuations of incidence beyond the established norm, uncommonly reaching epidemic proportions other than in areas or institutions where crowding favors transmission of the virus.

Gundersen's[30] experience in Norway and that of Ringberg[73] in Denmark illustrate admirably the secular variations in the incidence

of mumps, an excess prevalence occurring roughly every 7 or 8 years. Much the same behavior has been evidenced by mumps in the United States Army, other than for the abnormal factor of wars[90a] (Fig. 1). Definite outbreaks sometimes occur in rural regions but the true epidemic potentialities of the disease are best manifested in military populations.

Seasonal Fluctuations. Mumps can occur at all times and in all places, but under endemic conditions a regularly increased incidence occurs in winter and spring, especially during the months of March and April;[12b] and some three-quarters of epidemics occur at this time.[78] The incidence drops to very low levels during the summer. No better explanation of the seasonal variation in prevalence of mumps can be offered than is possible for other common communicable diseases. To the usual considerations of weather and closer contact in winter months comes a suggestion that physiologic changes in the host may be a factor. For 3 successive years, Johnson and Goodpasture[43c] were forced to interrupt their studies on experimental mumps of the monkey because of inability to induce the clinical disease with any degree of regularity from July through September, although using virus suspensions which they had every reason to believe were satisfactory.

Host Distribution. In civilian life and under ordinary conditions sex has no influence on susceptibility to mumps.[19] The reported differences in racial incidence[90b] seem to be dependent more upon opportunities for infection than upon genetic influences. For example, in the World War the rate for mumps among white enlisted men was 49.99 per 1000 and for colored troops 134.75, a fact which finds partial explanation at least in the reported statistics from Alabama[82] from 1926 through 1934, where the rate for colored is 10.4 and for white persons 31.3 per 100,000. In an Indian boarding school Tillim[89] observed an attack rate of 90%.

The commonest age of attack is at about 6 years. In Massachusetts,[12b] 88.6% of reported cases involve children less than 15 years of age.

Mortality Rates. Death rates for mumps are extremely low—0.12 per 100,000 over a period of 22 years in Massachusetts[12a]—and apparently even less than official records indicate. Investigating reported deaths from mumps in the state of New York, Williams[98] found many instances where the diagnosis was questionable. Some 20 of 65 patients who died had some variety of suppurative disease. Relatively few fatal infections were at the ages of greatest prevalence. An appreciable number of the patients who died were more than 65 years of age or infants, age groups with very low attack rates which would indicate a degree of severity much greater than clinical experience suggests.

Military Outbreaks. The influence of wars on epidemics of mumps[4] comes from the excessive recruiting of troops, so that large numbers of susceptibles are brought together at the same time. This factor is well illustrated by the continued high morbidity for mumps in the French Army, several fold greater than in the British Army. It is reasonable to suppose that the same proportion of recruits come from rural and urban districts but because of compulsory military service in the French Army larger numbers serve for short periods, with a consequent rapid turnover, in contrast to the long enlistments that characterize the British Army.

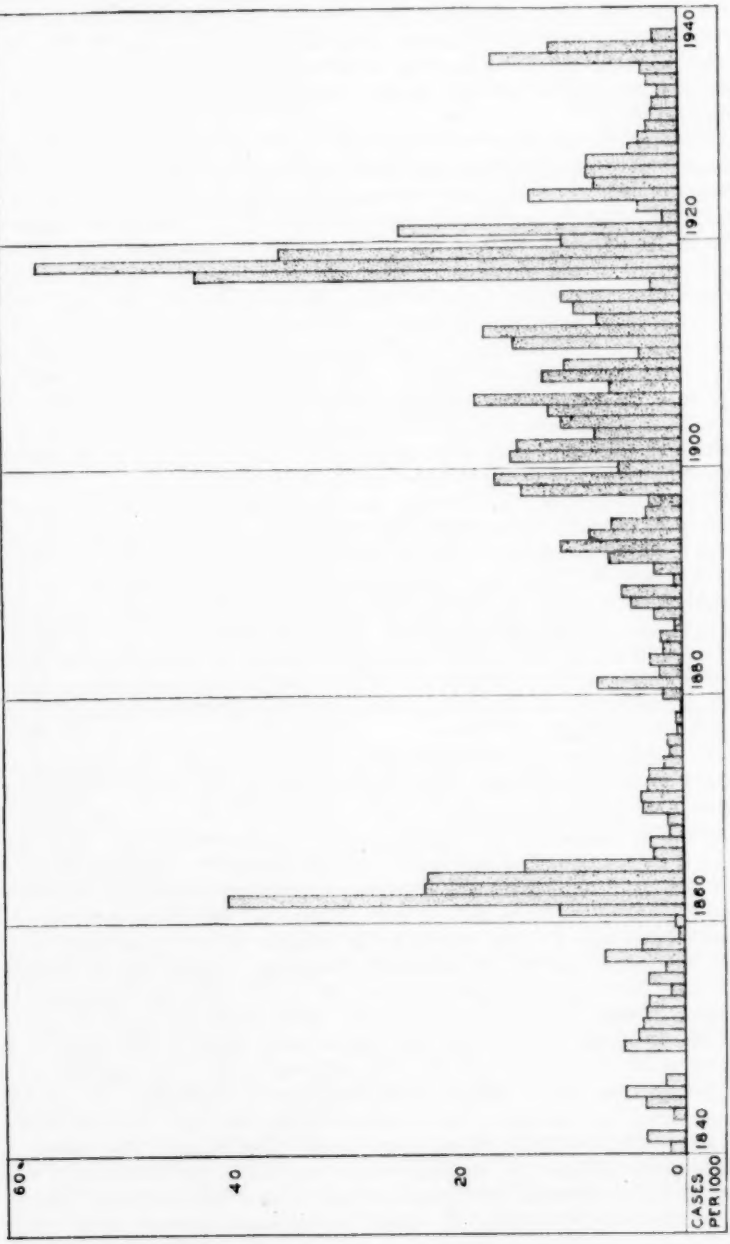

FIG. 1.—Attack rates for mumps, white troops of the United States Army, 1840 to 1938, lacking 1842, 1847 and 1848.

In the American Army, great epidemics of mumps occurred in both the Civil War and during the World War of 1918, with no marked disturbance during the course of the Spanish-American War, since mobilization took place in late spring and summer, and additions to the army did not extend into the mumps season. The importance of this factor is emphasized by Cook[13] who found that men entering the navy in the fall and winter months suffer a much higher incidence of cerebrospinal fever during the first year than those entering during the spring and summer. The extreme susceptibility of recruit, for contagious diseases in general is brought out by Wheelis,[96] who showed that by far the highest rates occur during the first 2 months of service, and that this holds true for all seasons, although less marked in summer than in winter.

During the World War mumps was more prevalent in large camps than in smaller and less densely populated organizations; and attack rates were directly related to whether troops were drawn from the rural South, or from industrial regions like the Eastern and New England states. In some instances attack rates were unusually great, 32% in Camp Wheeler.[71] In the course of recent years, attack rates in American Army practice have been about 10 per 1000,[90a] while civilian rates for all ages, in a state like Massachusetts, were 1.8 per 1000. Of course, reporting is much better in the army; Hedrich's[32] correction indicating that only about 12% of cases are officially notified in Massachusetts.

Administrative Control. Lacking a method for permanent protection, or satisfactory measures for treatment of the more serious manifestations which so frequently occur at a later age, attempts to prevent mumps in the individual exposed child of 5 to 15 years are under ordinary circumstances not advisable.

Susceptible children exposed at home may return to school 3 days later, this interval accounting for delayed symptoms from simultaneous exposure. Exclusion from school then follows from the fourteenth through the twentieth day, immune children continuing attendance. In our experience, quarantine of contacts has served to limit outbreaks in schools, hospital wards, and institutions more effectively than for almost any other of the common communicable diseases of childhood.

Isolation of patients with mumps is sometimes practiced for unreasonable periods, as long as 21 days. Laboratory experiment and field experience show that communicability rarely extends longer than the duration of the swelling; which makes at least 7 days' isolation, and until the swelling of the salivary glands has receded, a good general recommendation, sometimes necessarily extended by late appearance of a second involved gland.

The extensive outbreaks of mumps that so often occur in quickly mobilized troops could conceivably be avoided by not concentrating recruits from rural regions, but mingling newly enlisted men from city and country to give a mixture of immunes and susceptibles. A practice in communicable disease hospitals applicable to troops is to enter on the service record a note of previous attacks of communicable disease[23] which forms a basis for quarantine and aids in the diagnosis of doubtful infections. Once an outbreak is well under way, quarantine is essentially useless under military conditions because of the numerous and repeated contacts. Furthermore, it interferes with military activities so greatly, that it is only justified in the attempt to curb an incipient

outbreak. Daily inspection of known immediate contacts for early manifestations of the disease aids in prompt isolation. The measures outlined are equally applicable to fixed populations under civil conditions.

Specific Prevention. The serum of patients convalescent from mumps is used under special circumstances to prevent the disease, and has been recommended as a measure for modifying or eliminating the severer effects that tend to follow the initial parotitis.

The usefulness of the method is restricted by the short protection afforded, and the limited availability of the serum. It finds application for children in poor health or suffering from other diseases;[76] in avoiding the disorganization of activities that follows an outbreak of mumps in summer camps;[88] in hospital outbreaks;[31,72] in boarding schools;[100] and under military conditions or in institutions[6] where an outbreak is recognized early with promise of successful control.

Although whole blood was first used[35] for passive protection and has been employed by some others,[1] the separated serum is more practicable because it can be stored for use as required. Blood is preferably collected 2 to 3 weeks after clinical attack, but 3 months is satisfactory and more remote infections serve in necessity. The usual dose is 10 cc. administered intramuscularly, although some have used 20 cc. and others as little as 3 cc.

The manner in which mumps spreads and the short period of infectiousness before clinical recognition suggest that prompt use of convalescent serum should give encouraging results, which is corroborated by a considerable personal experience with outbreaks in hospital wards and institutions, and is an opinion held rather broadly.[45,97] Skrotsky,[79] for instance, observed that 177 of 179 exposed susceptibles escaped infection; Kutscher[46] in a summer camp for boys aged 9 to 16 years protected all but 1 of 52 who had not had mumps.

The administration of convalescent serum to patients with clinical parotitis, in an effort to prevent other manifestations of the disease, lacks proof of any worthwhile value. Some reports are of individual cases[27,57] and other series[36,49] are brief and inadequately controlled. The difference of 20% and 29% for orchitis in Iversen's[40] series of treated and untreated patients lacks statistical significance. If the method has any value it should come from immuno-transfusion[16] of large amounts of blood. However, most of the evidence obtained in the laboratory by means of animal experiments and tissue cultures[74] points to the fact that once a virus has attached itself to a cell or passed within a cell, antibodies in the therapeutic serum encounter great difficulty in reaching them in effective doses.

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